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The Influence of Respiratory Gas Mixtures on Arterial Pressure and Vascular Reactivity in "Normal" and Hypertensive Dogs

By IRVINE H. PAGE, M.D., AND FREDERICK OLMSTED, A.B.

The reactivity of the vascular tree to chemical stimuli is of fundamental importance in both hypertension and shock. Refractoriness and hypotension can be elicited by stimuli arising in the sympathetic ganglions as a result of their stimulation by carbon dioxide. "Total" autonomic ganglionectomy thus prevents the appearance of refractoriness and aids in production of the supernormal hypotensive response to carbon dioxide.

Dogs with renal experimental hypertension differ from those with neurogenic hypertension in that they react normally to carbon dioxide and several other vasoactive substances. The neurogenic hypertensives exhibit greatly heightened depressor responses and hence vasomotor activity. The mechanism for refractoriness is intact in both groups of animals and does not appear overactive in either. The neurogenic mechanism for the production of refractoriness is lost in the sympathectomized animal.

THE RESPONSE of the blood vessels to chemical and nervous stimuli is a fundamental problem in hypertension and shock. If, as in terminal shock, responsiveness diminishes or disappears[1] vascular collapse is imminent. On the contrary, hypersensitivity of the blood vessels in hypertension has not as yet been clearly demonstrated. If it exists, then increased nervous or humoral stimulation would not necessarily be a prerequisite to the development of hypertension. This paper records our initial steps in a systematic study of this problem.

Our experiments consisted of determining in dogs under light pentobarbital anesthesia and curare the effects on arterial pressure and vascular reactivity of carbon dioxide–oxygen mixtures administered by a respirator. When a range of carbon dioxide–oxygen mixtures was found which regularly reduced or abolished responsiveness, we sought for the mechanism of this refractoriness.

To control blood gas content and pH, it was necessary to paralyze compensatory respiratory mechanisms by an agent such as curare, and to supply gases by artificial ventilation. Stimuli used to test reactivity were adrenaline, noradrenaline, barium chloride, angiotonin, veratrum alkaloids (Veriloid), tetraethylammonium chloride (TEAC), and less often, sodium azide, sodium nitroprusside, renin, and tyramine.

Although not used in the first of this work, pentobarbital was employed in later experiments, since small amounts (20 to 35 mg. per Kg.) apparently did not alter the results decisively. In studies where the spinal cord was severed, no anesthesia was required.

METHODS

Mongrel dogs were given 20 to 30 mg. per Kg. of pentobarbital intravenously, and a tracheal catheter

From the Research Division of the Cleveland Clinic Foundation and the Frank E. Bunts Educational Institute, Cleveland, Ohio.

TABLE 1.—*Examples of the Action of CO_2-O_2 Mixtures on Reactivity of Normal Dogs*

No.	% CO_2	B.P. Change	Adren.	Nor-adren.	Azide	Nitro-prusside	Barium Chloride	TEAC	pH	B.P.	Remarks
1360			12	36		−18	8			104	
	5	26	0	32		−20	10			122	
	15	28	8	10		−34				142	
	5	8	12	26		−26				126	Curare given
	15	−36	4	18		−18	0			118	
1326			42	106	+10−20	−62	22			124	Curare given
	30	−44	0	4	−14	−14	0		6.93	116	
	30		30	56		−62					Both carotid sinuses ou
			0	20		−26	14		1.81		
1273			36	52						120	Carotid sinuses out
	40	−76	0	0						140	Curare
	50			14						154	
	50		0	0						192	
	50		0	0						152	Vagus nerves cut
	50		8	24				−68		90	
1274			+18−32	24			22			172	Carotid sinuses out
	50	−106	16	48						72	
	60		8	22					6.63	80	
	Air		24	50						126	
	40	−82	18	50						110	
	60		0	8						120	
	50	−36	6	28					6.64	72	
			4	16			10	−14		32	Vagus nerves cut
1275			28	92			20			140	Curare
	50	−70	0	20			20			200	
	O_2		48	116						150	
			46	108						190	Carotid sinuses out
	40	+66−102	8	18			16			206	
	40		0	0				+18−42		260	Vagus nerves cut
	40		16	32				48		196	
	40		32	62			48			194	
	O_2		60	100						136	Adrenalectomy
	40	−44	20	4			18		6.63	116	
1268			30	88						120	Curare
	20		36	76						92	
	30		34	70						102	
	50		18	42						140	
	Air		44		−46					142	
	40		18	44	−10					142	
1324			24	62	−28	−24	14			156	Curare
	30	−18	8	26	−4	−4	10		6.83	148	

with inflatable cuff tip inserted. The femoral artery was cannulated, connected to a mercury manometer, and Paritol* was used as an anticoagulant. The femoral vein received the test injections. A drip of saline was constantly given into a vein on the opposite side of the body. The test doses were adrenaline, U.S.P., 2.5 γ; noradrenaline, base (Arterenol),† 10 γ; barium chloride, 9 mg.; angiotonin,

* Paritol was kindly supplied by Dr. Joseph Seifter of Wyeth, Incorporated. We find that a saline solution containing 50 to 75 mg. is an entirely satisfactory anticoagulant for the manometer and tubing.

† Noradrenaline (Levophed) was kindly supplied by Mr. W. A. Curran of Winthrop-Stearns Company

5 cat units; tetraethylammonium chloride (TEAC), 5 mg. per Kg; sodium azide, 63 γ; sodium nitroprusside, 25 γ; tyramine, 1 mg.; Veriloid,‡ 20 to 30 γ.

After responses to these drugs had been established, dimethyl tubocurarine iodide was given until respiration ceased, and artificial ventilation was started. The dose of curare was considerably less than that required to paralyze autonomic functions.[2] During treatment with gas mixtures, two types of response were determined: (1) maximum change in arterial pressure elicited by gas inhalation, followed by admission of air; (2) changes in arterial pressure and responsiveness to test drugs during continuous inhalation for some 20 minutes.

Gas mixtures were prepared by allowing oxygen, carbon dioxide and/or nitrogen to mix in variable proportions in a rubber bag from the reducing valves of gas cylinders. The gas was bubbled through water to establish normal water tension. The intake of the respirator pump was connected to the rubber balloon. The respirator oxygen (and thereby the carbon dioxide or nitrogen) was measured with a paramagnetic oxygen analyzer.[3] The whole blood pH from samples obtained by femoral artery puncture was determined with a Leeds and Northrup number 7660 potentiometer and a Claff glass electrode at 38 C.[4] Total blood carbon dioxide content was determined by the lactic acid method of Van Slyke[5] from arterial blood drawn and kept under oil, immediately refrigerated and analyzed within five minutes. The oxygen saturation of arterial blood was determined by the reflectometer of Brinkman.[6] Neurogenic hypertension was produced by section of the aortic depressor nerves and removal of both carotid sinuses with a technic taught us some years ago by Dr. Keith Grimson. Renal hypertension was elicited by the cellophane perinephritis method.[7]

Results

The Effect of Carbon Dioxide–Oxygen Mixtures on Arterial Pressure

In normal dogs under curare, change from ventilation with air to mixtures of oxygen and 15 to 60 per cent carbon dioxide, after a latent period of 30 to 60 seconds, resulted in a sharp fall (40 to 80 mm. Hg) in blood pressure which lasted often throughout the administration of gas. Ordinarily, pressure rose from the initial low levels on carbon dioxide to intermediate levels some 20 to 30 mm. Hg higher and remained there. When the carbon dioxide concentration was increased further, i.e., to 50 to 60 per cent, arterial pressure again fell, but to a lesser degree. When air was readmitted, blood pressure usually rose quickly 40 to 60 mm. Hg; but in some animals, especially after long exposure, several hours were required for restoration of normal arterial pressure.

The quantitative variability in pressure response to carbon dioxide mixtures was similar to that observed previously with the test drugs.[8] Therefore, averages were used in making comparisons and only large differences were considered significant under the various experimental conditions (table 1). The average response of normal dogs, under curare and artificial ventilation, to 15 per cent carbon dioxide was −20 mm. Hg (range +12 to −40), and to 30 per cent carbon dioxide, −40 mm. Hg (range +33 to −106). Average responses to other test drugs are given in table 2.

Table 2.—*Examples of the Range of Normal Reactivity (Arterial Pressure in mm. Hg) in Dogs**

	Low	Medium	High
Adrenaline	4	30	72
Noradrenaline	20	73	118
Barium chloride	0	21	64
TEAC	−20	−43	−60
Veratrum ("Veriloid")	0	−31	−68
Sodium Azide	−26	−42	−64
Angiotonin	4	22	48

* Dosage given in text.

Repeated tests with 15 and 30 per cent carbon dioxide, in which the gas mixture was given until maximum hypotension had been attained, followed by readmission of air, showed the hypotension to be less severe during the first test. In subsequent trials carbon dioxide inhalation could be repeated at least eight times with relatively consistent depressor responses. In some, however, the initial response was a rise in pressure (4 to 30 mm. Hg) followed by a fall of usually greater magnitude.

This normal variability of response emphasizes again the necessity for many experiments and for recording blood pressure changes to show the *entire course* of the vascular response, rather than for measurement at random intervals with the auscultatory method (table 1).

An attempt was then made to influence normal responses to carbon dioxide by atropine

‡ Veriloid was kindly supplied by Dr. Philip Bates of the Riker Chemical Company.

and by various operations on the nervous system well after recovery from operative trauma.

Vagotomy in 4 normal dogs did not notably influence response to carbon dioxide, nor did atropine sulfate (1.2 mg.). Removal of both carotid sinuses was without significant effect. Combined vagotomy and carotid sinus resection the day before an experiment did not increase hypotensive reaction to carbon dioxide in 6 dogs.

Bilateral paravertebral ganglionectomy, from T1 to T9 inclusive, nearly doubled responses in 5 otherwise normal animals; total sympathectomy in 9 increased responses even further (table 3). In one sympathectomized animal, for example, 15 per cent carbon dioxide lowered blood pressure 88 mm. Hg, in comparison with a reduction of 20 mm. in normal animals.

Atropine in most cases somewhat reduced the fall, chiefly by preventing exaggerated cardiac slowing due to the vagus nerve hyperfunction in sympathectomized dogs. This was also noticed in dogs with destroyed spinal cords, in which a marked rise, rather than the usual fall, followed atropine. The effects of atropine on carbon dioxide response were never as impressive as might have been anticipated from the high vagus tone.

Cardiac denervation, consisting of ganglionectomy from T1 to T9 and section of cardiac vagus fibers in the mediastinum increased response of 6 dogs to carbon dioxide, but only slightly more than ganglionectomy alone. In one normal dog, response to 15 per cent carbon dioxide was +18 mm. Hg before cardiac denervation and −42 mm. Hg after. Following section of carotid sinus nerves a week later by

TABLE 3.—*The Effect of Sympathectomy and Cardiac Denervation on Arterial Pressure Response to CO_2-O_2 Mixtures*

Dog No.	% CO_2 inhaled	B.P. Change	B.P. Average	Remarks
1336	30	−90	138	Sympathectomy completed 1 day before
	20	−106	180	
	15	−88	164	
Atropine		+68	174	
	15	−86	162	
Vagus nerves anesthetized	15	−64	164	
1358	15	−46	106	Same dog 1 month later
Atropine		+6	136	
	15	−26	108	
Benadryl	15	−50	160	
1341	15	−36	110	Sympathectomy completed 5 days before
	30	−56	112	
Atropine		+14	106	
	15	−22	112	
1357	15	−20	98	Same dog 1 month later after carotid sinus denervation (?)
1328	30	−78	124	Sympathectomy completed 3 days before
	20	−82	164	
	10	−60	152	
1339	15	−46	174	Bilateral ganglionectomy T1 to T9
	30	−76	170	
1342	15	−42	170	Cardiac denervation
Atropine		−34	170	
TEAC 10 mg./Kg.	15	−30	140	
	15	−50	128	Carotid sinus nerves cut 1 month later

Dr. James McCubbin, with complete recovery, response to carbon dioxide was −50 mm. Hg. The supersensitivity to carbon dioxide extends also to such depressors as sodium nitroprusside. Resection of carotid sinuses or severing vagus nerves in dogs whose hearts were denervated did not significantly affect responses. Nor did atropine greatly decrease the depressor effect to carbon dioxide itself.

Results in 7 animals whose spinal cords had been destroyed from C6 caudad several days previously, exhibited the greatly heightened responsiveness to carbon dioxide seen in those sympathectomized (table 4).

TABLE 4.—*The Effect of Spinal Cord Destruction from C6 Caudad on Response to CO_2-O_2 Mixtures*

No.	Per cent CO_2	B.P. Change	B.P.
1290	5	−66	150
1282	35	−84	120
Atropine		+54	142
	30	−66	136
1292			
Atropine	5	−28	120
	30	−38	94
	50	−62	126
1340	15	−34	82
	20	−60	100
$NaHCO_3$	20	−34	62

These experiments show that the vagus nerves and carotid sinuses ablated several days before the experiment failed to have decisive influence on depressor responses to carbon dioxide. But sympathectomy, whether associated with cardiac denervation or "total," greatly augmented carbon dioxide response. Destruction of the spinal cord did much the same thing.

To pursue further the significance of autonomic ganglions in the response to carbon dioxide, 6 normal dogs were treated with 10 to 20 mg. tetraethylammonium per Kg. after responsiveness to carbon dioxide had been determined. This dose produces blockade but is not enough to elicit pressure rise from the tetraethylammonium itself. It is a compromise dose which should bring out any effect this type of blockade would have on carbon dioxide as a depressor. No other test drugs were used in these experiments. Repeated tests with 15 and 30 per cent carbon dioxide showed partial blockade with tetraethylammonium in normal dogs and did not significantly influence the initial blood pressure fall; nor, as we shall see later, did it prevent development of some refractoriness when 50 per cent carbon dioxide was inhaled.

The effects of prolonged administration of carbon dioxide in dogs under influence of tetraethylammonium and other blocking agents have been studied and will be considered in another communication.

Since the adrenal glands might influence response by compensating for blood pressure fall from carbon dioxide, the glands were removed. In one experiment, for example, after carotid sinus denervation, 40 per cent carbon dioxide lowered pressure 101 mm. Hg. Vagus nerves were then cut and autonomic ganglionic transmission diminished by injection of 10 mg. tetraethylammonium per Kg., and finally both adrenal glands were removed. Now 40 per cent carbon dioxide lowered blood pressure 44 mm. Hg. We had expected a greater pressure lowering from the removal of a possible compensatory mechanism, but a lesser one occurred.

Elicitation of Vascular Refractoriness

Various tubocurarine derivatives were used to paralyze respiration. All produced fall in arterial pressure if injected rapidly but little or none if given slowly, in which case reactivity of the vascular tree usually did not change. It was sometimes slightly reduced or even notably increased.

In normal animals, a few minutes after initial inhalation of the gas mixture, responsiveness to most test drugs fell sharply or disappeared when concentrations of carbon dioxide from 30 to 60 per cent were given. Usually, partial refractoriness was elicited within a short time by concentrations as low as 15 to 20 per cent. Refractoriness lasted throughout carbon dioxide administration and often disappeared promptly when air or 100 per cent oxygen was substituted, especially when this ventilation change was accompanied by sharp blood pressure rise. In some, hyperreactivity appeared a few minutes after arterial pressure

had risen to normal, only to disappear again after 10 to 20 minutes.

Adrenaline responses were more readily abolished than those of noradrenaline. More peripherally acting myotropic substances (angiotonin, renin, barium chloride) ordinarily continued to give some response when adrenaline and noradrenaline were almost inactive (fig. 1). But when refractoriness was established, both pressor and depressor drugs exhibited strongly reduced responses.

A purified veratrum alkaloid (Veriloid),

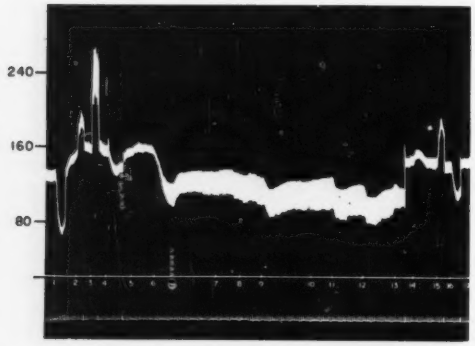

FIG. 1. Refractoriness in a normal dog resulting from inhalation of 30 per cent carbon dioxide. (1) Nitroprusside. (2) Adrenaline. (3) Noradrenaline. (4) Sodium azide. (5) Barium chloride. (6) 30 per cent carbon dioxide. (7) Adrenaline. (8) Noradrenaline. (9) Nitroprusside. (10) Barium chloride. (11) Sodium azide. (12) Nitroprusside. (13) pH 6.93. Air given. (14) Adrenaline 35 minutes later. (15) Noradrenaline. (16) Sodium azide. Exclusion of both carotid sinus nerves altered this pattern insignificantly.

known to reduce blood pressure in part by way of the von Bezold reflex, was greatly affected by carbon dioxide refractoriness. For example, an amount of alkaloid which reduced blood pressure 30 mm. Hg was ineffective when noradrenaline response was reduced by carbon dioxide from 60 to 16 mm. Hg.

The initial tetraethylammonium chloride injection while animals were refractory often caused an arterial pressure rise rather than the usual fall seen in normal animals. Perhaps the most common effect with higher concentrations of carbon dioxide was a rise (average 25 mm. Hg) followed by a large drop (average 54 mm. Hg). More interesting, however, was the immediate partial return of responsiveness to adrenaline and noradrenaline upon tetraethylammonium chloride administration. However, return to the response level before carbon dioxide was incomplete, as evidenced when room air was substituted for carbon dioxide when even greater responses occurred.

The Effects of Anesthesia and Different Concentrations of Carbon Dioxide. In normal dogs under pentobarbital anesthesia but without curare, 5 to 15 per cent carbon dioxide customarily caused marked hyperventilation, increased pulse pressure and rise in arterial pressure (10 to 28 mm. Hg). Injection of curare with the same concentrations of carbon dioxide then caused a 10 to 30 mm. Hg fall, often followed by a 10 to 20 mm. Hg rise. Prolonged breathing of 15 per cent carbon dioxide – oxygen mixture responsiveness reduced slowly in some, quickly in others. Higher concentrations simply caused greater fall in arterial pressure and more marked refractoriness.

Response to 30 per cent carbon dioxide was determined in several dogs with spinal cord sectioned at C6. Curare was then given, and finally 25 mg per Kg. body weight of pentobarbital. In this way, effect of the anesthetic could be ascertained without interference by pain and apprehension. Response to carbon dioxide was essentially the same before and after anesthetic.

Effects of High Nitrogen Gas Mixture. Experiments were performed with mixtures of 90 to 98 per cent nitrogen and 10 to 2 per cent oxygen, both with and without curare. With, for example, a mixture of 95 per cent nitrogen, average blood pressure rose 40 mm. Hg or more. Even though the blood became extremely cyanotic, reactivity did not change significantly. The same animal given 25 per cent carbon dioxide rapidly became refractory. In another animal, breathing stopped for about 30 seconds but responsiveness was not lost.

The experiments show clearly that nitrogen inhalation does not produce the changes in reactivity elicited by carbon dioxide.

Mechanism of Vascular Refractoriness Elicited by Carbon Dioxide

Following demonstration that carbon dioxide could reproducibly elicit refractoriness, the

mechanism by which it did so was sought. As we have noted, simple asphyxia with nitrogen failed in brief studies to cause consistent reactivity changes.

Since the carotid sinuses are known to participate in carbon dioxide responses[9, 10] the next step was to determine the extent of this participation. Excision of both bifurcations of carotid arteries the day before, or section alone of carotid sinus nerves, failed to prevent refractoriness. In addition, the degree of hypotensive reaction to carbon dioxide did not change when the sinuses were inactivated immediately after quantitation of the carbon dioxide response (twelve experiments).

Since carbon dioxide might have influenced liberation of adrenaline and noradrenaline, the adrenal glands were removed, either before or during the experiment (seven studies). We were unable to show significant adrenal participation in vascular refractoriness elicited by carbon dioxide.

In sympathectomized dogs, atropine (1.2 mg.) usually caused immediate pressure rise of about 70 mm. Hg or a rise followed by a fall. The fall from carbon dioxide was normally lessened by atropine in dogs with destroyed spinal cord and consequent high vagus tone. Thus, cholinergic nerve fibers are probably not responsible for hypotension after carbon dioxide administration, especially since refractoriness can also be produced in atropinized dogs.

Autonomic Ganglionic Blockade with Tetraethylammonium Chloride. The autonomic nervous system seemed to be concerned in the development of carbon dioxide refractoriness. As shown above, refractoriness may be in part abolished by blocking autonomic ganglions with tetraethylammonium.[20] We reversed the procedure, giving partial or complete blocking doses (10 to 30 mg. per Kg.) of tetraethylammonium before attempting to produce refractoriness. In most animals, the gas mixture then produced only moderate loss of reactivity, but in others, especially when 60 per cent carbon dioxide mixture was used and blood pH fell to 6.70, some refractoriness unquestionably appeared. Also, despite blockade of vasomotor impulses with tetraethylammonium, a fall in arterial pressure regularly occurred with carbon dioxide, similar to that in untreated animals.

Surgical Sympathectomy and Refractoriness. Evaluating the effect of surgical sympathectomy as originally performed in cats by Cannon, Lewis and Britton[11] seemed the next logical step. Fifteen sympathectomized dogs (ganglionated chain removed from T1 through L4 by Dr. Charles Ballinger assisted by Mr. George Wilson) were studied. In these, the gas mixture failed to induce refractoriness, except in 2 where autopsy showed that certain ganglions had been left intact. Variations occurred: for example, about 20 per cent reduction in reactivity was observed in one when 60 per cent carbon dioxide–oxygen was given, while almost the same increase was seen in another under the same conditions.

Great differences in initial reactivity make comparison of sympathectomized dogs with normal animals difficult. Even low carbon dioxide concentrations cause severe hypotension in sympathectomized animals, 15 per cent often having much greater effect than 50 per cent carbon dioxide in normal animals. When the pressure ranges from 20 to 40 mm. Hg after a quick drop, reactivity is difficult to test simply because with the slowed circulation drugs do not reach the blood vessels at normal rate. But even with low pressure, which often militates against maintenance of reactivity, sympathectomized dogs keep their responsiveness (table 5).

Because of supersensitivity in these animals, the doses of depressor drugs, sodium nitroprusside and azide, were cut to 25 per cent of the usual test quantity.

It was established that "total" surgical sympathectomy largely prevented refractoriness. Blood pH fell to the same level (6.70) as in nonsympathectomized dogs; strong evidence that reactivity and pH do not correlate (fig. 2).

We convinced ourselves that curare and artificial respiration in most cases failed to alter responsiveness in sympathectomized dogs. When 15 per cent carbon dioxide was administered, vagus tone, as estimated by the response to atropine, was not strikingly high, and atropine did not alter drug responsiveness. But, when 50 or 60 per cent carbon dioxide was given these dogs, vagus tone must have

been very high because atropine caused sharp pressure rises somewhat decreasing the hypotensive action of carbon dioxide. Here again

TABLE 5.—*Average Response to Adrenaline and Noradrenaline during 30 Per Cent CO_2 Administration*

	Avg. B.P.	Average B.P. Fall after CO_2	Per cent Fall after CO_2	Response to	
				Adrenaline	Noradrenaline
	mm. Hg	*mm. Hg*		*mm. Hg*	
Normal	116	−40	34	0	4
Renal hypertension	178	−70	40	4	18
Sympathectomy	126	−80	65	20	50
Neurogenic hypertension	198	−110	55	42	68
Bilateral vagotomy	124	−50	40	2	12
Ganglionectomy T1-T9	150	−76	51	0	14
Carotid sinus out	144	−42	30	0	20
Cardiac denervation	120	−66	55	12	28

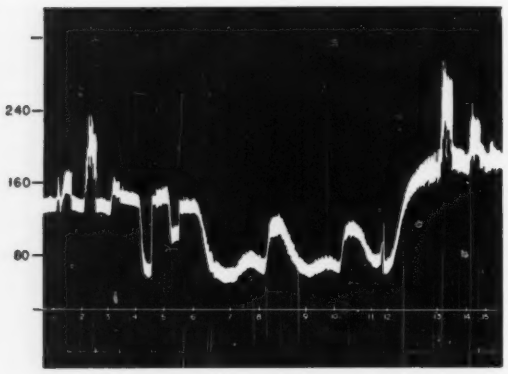

FIG. 2. The effect of 30 per cent carbon dioxide on vascular reactivity in a sympathectomized dog (No. 1328). (1) Adrenaline. (2) Noradrenaline. (3) Barium chloride. (4) Nitroprusside. (5) Sodium azide. (6) 30 per cent carbon dioxide. (7) Adrenaline. (8) Noradrenaline. (9) Adrenaline. (10) Noradrenaline. (11) pH 6.80. (12) Air. (13) Adrenaline. (14) Noradrenaline. (15) Adrenaline. This shows the relative maintenanace of responsiveness even after a very severe fall in arterial pressure and the period of supersensitivity when carbon dioxide is withdrawn quickly followed again by normal or reduced reactivity.

neither the increase in pressure due chiefly to vagus release nor the blocking action of atropine had any effect on vascular responsiveness.

To determine if the augmented depressor response to carbon dioxide in sympathectomized animals might be histaminergic, we gave 10 mg. per Kg. of Benadryl. The response was unchanged. Thus neither atropine nor Benadryl has any decisive effect on their increased response to carbon dioxide. Tetraethylammonium chloride caused a transient pressure rise and slight rise in the average level. Concurrently, the responses to adrenaline, noradrenaline and angiotonin increased slightly, even though carbon dioxide administration was continued. Shifting to air increased blood pressure and vascular responsiveness still further.

While surgical sympathectomy prevented most of the refractoriness, tetraethylammonium was still able to increase responsiveness somewhat, though perhaps no more than would occur from the release of any other compensatory mechanisms which restrain changes in arterial pressure and are not abolished by surgical sympathectomy.

Spinal Cord Section. Section of the cord at C6 three days before the experiment in order to interrupt sympathetic outflow also eliminated pain and need for anesthesia. At this level of cord section, temporary occlusion of both common carotid arteries was not followed by pressure rise. The animals were given excellent nursing care and penicillin, essentials to this type of experiment.

These dogs were very sensitive to carbon dioxide. Inhalation of only 5 per cent led to considerable fall in pressure (60 to 70 mm. Hg), significantly reduced by preliminary atropinization. At these low concentrations of carbon dioxide, no refractoriness was observed. Raising concentration to 50 or 60 per cent greatly depressed arterial pressure, and then refractoriness occurred. Blood pH was also depressed to the low levels of normals given carbon dioxide.

As an incidental observation, an attempt was made to overcome refractoriness by intravenous administration of 9 mg. of cytochrome C,* without success. Breathing air, however, restored reactivity within a few minutes.

* We are grateful to Dr. Demetrius Decaneas and Dr. Samuel Proger for the cytochrome C.

Chronic Bilateral Vagotomy. Atropine and vagotomy in acute experiments did not greatly alter responses. Therefore, to reproduce the conditions of the denervation in neurogenic hypertensive or sympathectomized dogs, it was necessary to keep the animals alive a few days after vagotomy.

We first resected the vocal cords to prevent their falling together and thus made section of vagus nerves in the neck feasible. Most of these dogs died of pulmonary edema, hemorrhage or pneumonia within a day or so. Our problem was only partially resolved by preliminary gastroenterostomy, followed after healing by resection of vocal cords and vagus nerves. Antibiotics did not prolong survival.

Responsiveness to vasoactive drugs was normal up to a week after vagotomy. Depressor response to 30 per cent carbon dioxide was also normal. Refractoriness developed just as in normal dogs.

Thus, even after a relatively long time, bilateral vagotomy performed in the neck does not appear to alter responsiveness significantly.

Ganglionectomy, T1 to T9. Ganglionectomy from T1 to T9 inclusive was done in 6 animals because this area is included in cardiac denervation. Responsiveness to test drugs did not appear greatly changed (though somewhat increased) while the hypotensive action of 15 and 30 per cent carbon dioxide was about doubled. When in brief studies the vagus nerves and then the carotid sinuses were anesthetized by local injection of Novocain, there was still no change. Thus the augmented response to drugs in totally sympathectomized dogs is not due alone to ganglionectomy from T1 to T9, nor to short-lived blocking of vagus nerves and carotid sinuses. Moderate refractoriness developed in these animals.

Long Exposure to Low Concentrations of Carbon Dioxide. Since refractoriness appeared within a few minutes when high concentrations of carbon dioxide were used, whether or not lower concentrations over a longer time could have the same effect is pertinent.

A mixture of 10 per cent carbon dioxide and 90 per cent oxygen was given for six hours after curarization. Blood pH stayed at 7.14 (see table 7; 1333, for example). This carbon dioxide–oxygen mixture did not depress the average arterial pressure level. After an hour, response to adrenaline and noradrenaline was reduced about one half and shortly thereafter fell further but did not disappear. The depressor substances, azide and nitroprusside, also lost potency, until after six hours they lowered blood pressure one half to one third as effectively as before. After air replaced the gas mixture return of responsiveness was much slower than in our brief experiments. Often several hours were required for full restoration of reactivity.

The Change in Blood pH. The older literature suggests that blood pH directly modulates vascular reactivity. Consequently, we measured it repeatedly throughout all experiments. When 50 per cent carbon dioxide–oxygen mixtures were administered, the pH average was 6.71. Total carbon dioxide averaged 30.8 mM. per liter, with an average variation of 0.7 mM. per liter.

The ease and reproducibility with which a pH of 6.7 was obtained encouraged us to use this measurement chiefly to determine whether ventilation with the gas mixture was adequate and whether leaks were present, chiefly around the tracheal tube.

The pH bore no relationship to vascular reactivity. For instance, after sympathectomy, the same low pH value was reached during carbon dioxide inhalation as in normal animals, but refractoriness did not appear. It may appear in normals after prolonged exposure to low concentrations of carbon dioxide but without further change from the initial lowering to pH 7.14. Again, when responsiveness reappeared after giving tetraethylammonium, blood pH did not change toward normal.

We attempted to duplicate the carbon dioxide phenomena by infusion of N/10 hydrochloric acid with the dog under curare and artificial respiration, and failed. In one dog, for example, after 250 cc. had been given by vein, blood pH was 7.18, with response to test drugs unchanged. Within 30 minutes, 500 cc. N/10 hydrochloric acid had been given, vascular reactivity was somewhat increased instead of decreased. After 750 cc., blood pH was 7.02 and arterial pressure had begun to fall to

dangerously low levels. During this period responsiveness was reduced and the animal died shortly thereafter. Other animals behaved similarly.

We could not reduce easily or rapidly blood pH to levels as low as those obtained with carbon dioxide. Vascular responsiveness was not lost until great amounts of hydrochloric acid had been given and arterial pressure was falling terminally. Lactic acid infusion in comparable quantity also did not reproduce the carbon dioxide effect. The entire picture was so different that there could be no doubt that giving a fixed acid fails to elicit the syndrome of carbon dioxide–oxygen inhalation.

Lack of Central Action of Carbon Dioxide in Producing Vascular Reactivity Change. These six experiments were performed with Drs. R. D. Taylor and W. Gallivan, for whose help we wish to express our sincere appreciation. The experimental method[12] consisted of perfusing a recipient dog's head with heparinized blood from a donor dog through the carotid artery and returning it by a jugular vein. By most careful dissection, all vascular connections between the recipient's head and body were severed, so that only the nervous system connected the two. Evans blue injected into either part showed no crossing over from head to body. Most results published in the older literature were obtained on preparations which almost surely leaked blood from head to body. The carotid sinuses in most experiments were removed and the vagus nerves often cut.

Neither partial asphyxia of the recipient's brain, caused by incomplete clamping of the blood delivery tubing, nor asphyxia of the donor altered markedly the response of the recipient's body to adrenaline, noradrenaline, or barium chloride, despite pressure rise (from 110 to 222 mm. Hg.)

The 60 per cent carbon dioxide–oxygen mixture was administered to the curarized donor dog while the curarized recipient received air or oxygen. The donor dog's blood pH fell to 6.71, average blood pressure fell 20 to 40 mm. Hg and refractoriness occurred. But the recipient's body remained reactive. Refractoriness in the donor rapidly disappeared when air or oxygen was readmitted (see table 6).

The carbon dioxide gas mixture was next given to the recipient's body and not to the donor's. The pH fell to 6.67 and refractoriness appeared, which was quickly abolished by

TABLE 6.—*Cross Perfusion Experiment**

Recipient Animal 7.7 Kg. (Carotid sinuses inactivated, curarized)				Donor 19.5 Kg. (Curarized)			
Treatment	B.P.	Change	pH	Treatment	B.P.	Change	pH
	mm. Hg				*mm. Hg*		
Adrenaline	120	66		None	180		
Noradrenaline	124	58					
Adrenaline	128	58					
Noradrenaline	126	54					
Response of recipient	140	−22		50 per cent CO_2	248	−68	
				60 per cent CO_2	224		6.71
Adrenaline	134	66		Adrenaline	256	16	
Noradrenaline	94	62		Noradrenaline	252	24	
Intra-arterial adrenaline	126	−44		Air			
50 per cent CO_2	92	0		Adrenaline	204	32	
Adrenaline	90	10	6.67	Noradrenaline	204	44	
Noradrenaline	98	26		Adrenaline	212	40	
Air							
Adrenaline	66	34					
Adrenaline	68	46					
Noradrenaline	80	58					
Adrenaline	80	66					

* Experiment No. 1286

giving air. Thus, while pH fall and appearance of refractoriness regularly follow administration of carbon dioxide–oxygen gas mixtures to the bodies of both donor and recipient, it was not produced in the recipient's body by perfusing its head with the same blood which caused refractoriness in the donor's body.

Spontaneous Refractoriness in Dogs. Dogs occasionally exhibit moderate refractoriness persisting continuously for weeks or months which then, unaccountably, disappears. It may be marked; for example, dog 1337 responded to adrenaline with a fall of 12 mm. Hg. Depressor responses to other drugs were also minimal. The animal was curarized and given artificial respiration without marked change in reaction to adrenaline, noradrenaline or barium chloride. Then tetraethylammonium was given in the hope that it might, as in normal dogs, augment responsiveness. But even 50 mg. per Kg. given in 10 mg. per Kg. doses failed to do so. Even the tetraethylammonium itself failed to lower blood pressure more than 20 mm. Hg or raise it more than 18 mm. Hg, very small changes indeed either way.

Fifteen per cent carbon dioxide–oxygen mixture lowered blood pressure only 10 mm. Hg; 30 per cent raised it 24 mm. Hg and elicited moderate additional refractoriness. Fifty per cent carbon dioxide first lowered pressure 46 mm. Hg but pressure quickly returned to normal, with complete refractoriness except to barium chloride. Blood pH fell to 6.75, analogous to values for normals under Pentothal but without curare.[13]

To see if more complete blockade of ganglionic transmission could be secured than with tetraethylammonium alone, 40 mg. per Kg dimethyl piperidine was given.[14] A rise of 58 mm. Hg occurred, but the adrenaline and barium chloride response was unchanged. Thirty per cent carbon dioxide again elicited refractoriness.

Thus autonomic ganglionic blockade and artificial respiration with oxygen and carbon dioxide failed to alter significantly the spontaneous refractoriness of this dog. This state may appear without warning, and so far, we cannot overcome it. The example given is drawn from many; the phenomenon is not unusual and doubtless has confused some types of physiologic and pharmacologic experimentation.

Comparison of Response to Carbon Dioxide–Oxygen Mixtures

Neurogenic and Renal Hypertensive Dogs. Concentrations of oxygen and 30 per cent carbon dioxide were selected as standard test doses, because in normals under pentobarbital-curare fall in blood pressure conveniently ranged from 20 to 40 mm. Hg. After artificial respiration was established and responsiveness tested, 30 per cent carbon dioxide gas mixture was given for 15 to 25 minutes. Blood pH was measured after 15 minutes, and then air administered (table 7).

In normotensive controls, blood pressure fell sharply under carbon dioxide inhalation (20 to 40 mm. Hg), then regained a level not much below the initial one; yet responsiveness was greatly reduced to both pressor agents and the depressors sodium azide and sodium nitroprusside. The pH fell to an average of 6.83.

Average blood pressure of neurogenic hypertensive dogs often fell somewhat with pentobarbital anesthesia and curare. Consequently, the lightest anesthesia was given consistent with the animal's comfort. Pressure ranges of 200 to 260 mm. Hg were usual, falling to 190 to 220. Some of them were slightly less responsive to pressor agents than normal but exhibited heightened response to sodium azide and sodium nitroprusside. The 30 per cent carbon dioxide–oxygen mixture sharply depressed blood pressure[9] much more than in normal or renal hypertensive animals, both absolutely and percentage-wise. Pulse was greatly slowed, even after atropinization.

Pressor responsiveness to adrenaline and noradrenaline often increased slightly rather than decreased when concentrations of 20 and 30 per cent carbon dioxide were first given. In some hypertensive animals, adrenaline was depressor before carbon dioxide was given, but became pressor when arterial pressure had fallen somewhat from carbon dioxide. The more peripherally acting myotropic drugs (angiotonin and barium chloride) were less affected by carbon dioxide.

When 50 per cent carbon dioxide was given neurogenic hypertensives, pressure fall was extreme, with great slowing of heart rate. only to about half that level. Blood pH reached the same low levels of 6.80 to 6.93 as in normal animals. These neurogenic hypertensives

TABLE 7.—*Examples of Responses of Dogs under Different Experimental Conditions to Gas Mixtures*

No.	Time	% CO_2	B.P. Change	Adren.	Nor-adren.	$BaCl_2$	Azide	Nitro-pruss.	pH	B.P.	Wt.	Remarks
1324	10:08	Air		24	62	14	−28	−24		160	14.8	Normal
	10:19	30	−18	8	26	10	−4	−4	6.83	150		
	10:48	Air		26	80					140		
	1:10	Air		26	36	18	−16	−12		212		Carotid sinus out
1326	10:39	Air		42	106	22	+10−20	−62		116	11.4	Normal
	10:54	30	−44	0	4	0	−14	−14	6.93	116		
	2:02			30	56			−62		110		Both carotid sinuses removed
	2:12	30	−42	0	20	14		−26	6.81	80		
	2:35			6	34					80		
	2:42	Air		32	84			−58		110		
1328	2:07	Air	−78	30	94	34	−48	−78		126	17.1	Total sympathectomy 1 week before
	2:55	30		20	50				6.80	50		
	3:15	Air	124	100	54					174		
	3:25			16	72					144		
	3:56	20	−82							80		
	4:02	Air	64	46						146		
	4:11	10	−60	52			−30		7.12	82		
1319	9:36	Air		10	24	130	−98			198	8.3	Neurogenic hypertension
	9:45	10	14	16	68					190		
	9:58	30	−108	42	56	26			6.94	68		
		30		34	78					68		
	10:22	Air	98	8	34					168		
	10:47	20	−80	58	90	30			6.91	96		
	11:04	Air	66	18	50			−94		180		
1335	9:24	Air		−26	14			−136		212	12.4	Neurogenic hypertension
	11:14	30	−126	0	26			−72	6 79	158		Atropine-curare
	11:41	Air	40	20	22					172		
	2:42	Air		0				−108		242		
1322	10:45	Air		18	46	8	−34	−90		168	10.5	Renal hypertension
	11:07	30	−68	4	18	10	−26			120		
		30		4	24			−28	6.78	120		
	11:32	Air	48	20	40							
	11:57	20	−46	16	40	10						
1333	9:45	Air		30	64	14	−38	−54		120	14.2	Normal - curarized. Continuous CO_2 administration in low concentration
	10:24	10	0							140		
	11:02			18	36			−34	7.14	134		
	12:10			14	34	14	−24			120		
	2:20			12	20		−14	−10		136		
	3:04			14	50	16	−16	−14	7.14	122		

After swift descent, pressure hovered at 30 to 40 mm. Hg for a few minutes, then sometimes rose above control level; at other times it rose

became refractory to adrenaline, noradrenaline, barium chloride and nitroprusside, although it seemed more difficult to produce than in nor-

mals. Thus 30 per cent carbon dioxide lowered pressure more than normal, but was not so apt to block pressor-depressor responses.

Administration of atropine (1.2 mg.) to neurogenic hypertensive dogs before carbon dioxide resulted in pressure fall of about 26 mm. Hg and a smoothing out of some irregularities of the blood pressure trace usual in this group of animals. Severity of pressure fall elicited by carbon dioxide was not affected, nor was the extreme bradycardia abolished. But after the initial drop, higher pressure level recovery occurred in the atropinized dogs. Further, extreme slowing of the heart beat and irregularities at the depth of hypotension were eased. Refractoriness was established by high concentration of carbon dioxide after atropinization, as before.

Thus in the neurogenic, severely hypertensive dog, greatly augmented depressor responses occur to carbon dioxide, azide and nitroprusside, and but slightly reduced responses occur to the pressor drugs adrenaline and noradrenaline. In contrast with normal and renal hypertensive dogs, concentrations of 20 to 30 per cent carbon dioxide often slightly increased, rather than decreased, the pressor action of adrenaline and noradrenaline. But with higher concentrations refractoriness appeared just as in normals.

Average blood pressure of renal hypertensives (nine experiments) was not quite as high before anesthesia as that of the neurogenic hypertensives, but fell less under anesthesia. Their responsiveness was similar to that of normal animals despite elevated pressure. Exceptions were the abnormally great depressor responses to sodium nitroprusside and to 30 per cent carbon dioxide. The latter sharply depressed arterial pressure, much more so than normal. The absolute fall often approached that in neurogenic hypertensives but percentage fall was much less. Carbon dioxide elicited the same reduction in responsiveness to adrenaline, noradrenaline, barium chloride and angiotonin as in normals. Also, as in normals, blood pH fell to an average of 6.78.

Sympathectomized Dogs Contrasted with Neurogenic Hypertensive Animals. As a contrast to neurogenic hypertensives, in which carotid sinuses were removed and depressor nerves cut, a second series of 17 dogs was subjected to "total" sympathectomy by Dr. Charles Ballinger with the help of Mr. George Wilson. None were tested until three days after sympathectomy, and most from one to three weeks. It was noted early that once supersensitivity is established, it is not lost for many months, if at all.

These animals (tables 5, 7) all showed severe blood pressure fall on administration of 15 and 30 per cent carbon dioxide, greater than normals or renal hypertensives. While the absolute fall was less than that of neurogenic hypertensives, percentage fall was greater. The control response to adrenaline and noradrenaline usually was augmented and carbon dioxide only slightly reduced it, despite the resultant severely depressed arterial pressure. This contrasts with the reaction of neurogenic hypertensives in which initially reduced control responses were often heightened. The depressor drugs azide and nitroprusside were more active in sympathectomized dogs and neurogenic hypertensives than in normals. Blood pressures of these groups were so low at times from carbon dioxide that the injected drug must have reached its site of action slowly and so had reduced activity.

Thus the "totally" sympathectomized animal has the greatest hypotensive sensitivity to carbon dioxide, but fails, in contrast to normal, neurogenic and renal hypertensive dogs, to develop refractoriness. It differs from the neurogenic hypertensive dog not only in its greater sensitivity to the depressor action of carbon dioxide, but in failure of high concentrations of carbon dioxide to elicit refractoriness.

Discussion

Our study of the effects on the vascular tree leads us to believe that carbon dioxide has unique qualities. Even though conditions we have imposed in experiment rarely occur in patients, the fundamental reactions could exist in less dramatic form during shock or anesthesia.

Arterial pressure response to carbon dioxide

forms a vexing chapter in cardiovascular-physiologic literature. Almost every conceivable result has been recorded, and, unfortunately, is quite believable. Whether carbon dioxide is pressor or depressor seems dependent on the kind of animal, the kind and depth of anesthesia, the state of the nervous system, and finally, the concentration of carbon dioxide.[10] Our conclusions apply to conditions we imposed and do not pretend to invalidate previous work.

When concentrations of carbon dioxide from 5 to 10 per cent were given normal dogs under pentobarbital, blood pressure usually rose moderately (5 to 20 mm. Hg). But if curare and carbon dioxide with artificial ventilation were then given, a slight fall was usual. Higher concentrations (20 to 30 per cent) of carbon dioxide invariably produced severe hypotension, persisting after a slight recovery, until gas was discontinued. That high concentrations of alveolar oxygen were concurrent, and oxygen saturation of blood was normal, eliminate the possibility that any of this effect is due to hypoxia. Nitrogen inhalation did not produce comparable effects.

The evidence we have presented justifies the belief that the hypersensitivity after sympathetic ganglionectomy, rather than the change in blood pH, causes the marked increase in depressor action of carbon dioxide. Cardiac slowing contributes only slightly. We can confirm, after great experience, that after sympathectomy, carbon dioxide produces only hypotension.[15]

The few perfused dog's-head experiments demonstrate, in this preparation at least, that carbon dioxide hypotension is not mediated by the central nervous system. Administration of carbon dioxide to the donor's body always led to hypotension, but response of the recipient's body was insignificant. Only when the recipient's body received the carbon dioxide did its blood pressure fall. Since the donor's blood perfused in the recipient's central nervous system only, we must conclude that the central nervous system did not cause the hypotensive response to carbon dioxide.

Some have believed this action of carbon dioxide due to direct narcosis of blood vessel musculature. But this leaves unexplained how, after sympathectomy, the blood vessels and heart still react almost normally to chemical stimulants (adrenaline, noradrenaline, angiotonin, nitroprusside and barium chloride), although pressure fall following carbon dioxide be severe. Years ago, furthermore, Wiggers[16] showed that varying the carbon dioxide tension of alveolar air between 15 and 60 mm. did not directly affect amplitude, gradient or duration of systole or pulse pressure. The unusual ability of carbonic acid to penetrate cell membranes might account for its high activity compared with other acids.

Since atropine and the antihistamine Benadryl fail, except by indirect effect on heart rate, to alter carbon dioxide response, neither acetylcholine nor histamine liberation is a fundamental part of the hypotensive action.

Supersensitivity to carbon dioxide after sympathectomy, in the absence of better evidence, is due to removal of strong inhibitory action of the sympathetic nervous system. This function must be widely distributed because surgical removal of almost the whole ganglionated chain is necessary before maximum reactivity occurs. That the sympathetic system acts to inhibit, as well as to excite, coincides with our view as to how tetraethylammonium elicits supersensitivity.[17]

Schmidt and Pierson[18] showed that in vessels of the cat's medulla, carbon dioxide excess produced vasodilation only, with or without curare, and suggested that carbon dioxide has specific and delicate regulatory function on the caliber of these vessels, not necessarily dependent on blood pH changes. Furthermore, vasodilatation occurs in both intestines and extremities of cats perfused with blood aerated by lungs insufflated with 2 to 10 per cent carbon dioxide.[19]

Refractoriness elicited by carbon dioxide usually extends to all the drugs tested, is independent of the height of arterial blood pressure but dependent on the presence of sympathetic ganglions. If the period of carbon dioxide administration is not too long, refractoriness may easily be dispelled by air or oxygen. But when carbon dioxide concentration is low and long maintained, as in shock or

prolonged anesthesia, return of sensitivity may be long delayed.

When autonomic ganglions are blocked by tetraethylammonium[20] or coniine[14] instead of being surgically removed, the ability of carbon dioxide to produce refractoriness is reduced but not abolished. Refractoriness, when established, is partially relieved by tetraethylammonium. It is difficult to quantitate this release. The pressor responses during the action of carbon dioxide and tetraethylammonium were often as large as before carbon dioxide, but were not as great as those when air was substituted.

The extraordinary ability of carbonic acid, compared with other acids, to penetrate cellular membrane and alter internal pH of cell protoplasm is well recognized. Since the animal cannot respond by blowing off carbon dioxide because of curare and artificial respiration, the abnormal carbonic acid:bicarbonate ratio must be maintained in the ganglions. Increased intracellular acidity of the ganglions may be the immediate stimulus eliciting vascular refractoriness.

With autonomic ganglions removed, supersensitivity appears and carbon dioxide no longer induces refractoriness. In some, it apparently heightens the increased responsiveness. Blood pH falls to the same levels with or without the autonomic ganglions. In normal dogs the vascular tree is unresponsive, while in sympathectomized animals, it is highly sensitive. Since blood pH alone cannot determine reactivity, since tetraethylammonium partially blocks and sympathectomy completely blocks the development of refractoriness, and finally, since this occurs in the absence of the central nervous system, our belief arises that a refractory state results from inhibitory impulses resulting from stimulation of sympathetic ganglions. Just as in denervation supersensitivity, the sympathetic system, instead of causing excitation, has repressive and restraining function.

We have shown that "total sympathectomy" prevents the refractoriness of carbon dioxide and localizes the inhibitory function by stepwise ablation of various parts of the nervous system in the autonomic ganglions.

Burget and Visscher[21] were among the first to note that adrenaline activity in pithed cats was closely related to pH. From pH 6.9 to 8.0, response increased. Change of ventilation rate increased or decreased pH but a constant rate did not assure constant pH or carbonic acid. They attributed to pH a specific role in the responsiveness of the pithed animal to adrenaline. Our evidence also shows that low pH is associated with lack of responsiveness to adrenaline but that control of responsiveness rests not primarily in the blood pH but in the autonomic ganglions. Stavraky[22] found both hypo- and hyperventilation decreased the pressor action of adrenaline in cats, an action abolished by spinal cord destruction. Sympathectomy reduced rather than raised sensitivity in his preparations, this result presumably being due to the briefness of his experiments.

Blood pressure response pattern to carbon dioxide in renal and neurogenic hypertension possibly gives some insight into the mechanism involved. The height of arterial pressure varied little between the two, the neurogenic being moderately higher. The renal hypertensive response was normal to pressor agents, while the neurogenic was slightly reduced. Both exhibited large depressor carbon dioxide response but percentage fall in the renal group was little greater than in the normal (40 compared with 34 per cent) (table 5) contrasting with 55 per cent in the neurogenic hypertensives.

"Totally" sympathectomized dogs exhibited percentage fall (65 per cent) similar to neurogenic hypertensive animals. Thus neurogenic hypertensive and normotensive dogs with sympathectomy exhibit the same great sensitivity to the depressor action of carbon dioxide in contrast to the nearly normal reaction in renal hypertension. This suggests that loss of buffer mechanism in the neurogenic hypertensive, and the transmission gap in sympathectomized animals, accounts for their greater sensitivity to the hypotensive action of carbon dioxide. Apparently it is necessary to remove all buffer mechanism for significant changes in sensitivity to occur. Vagotomy performed several days or weeks before experiment, or removal of the carotid sinuses alone, had no appreciable effect.

There was a slight difference in the effect of high carbon dioxide concentrations on vascular responsiveness between renal and neurogenic hypertensive dogs. Renal hypertensive and normal dogs developed refractoriness about the same way. In the neurogenic group, however, with carbon dioxide 30 per cent or lower, responsiveness often increased when pressure had stabilized below the hypertensive control levels. Thus adrenaline, which was not unusually depressor when control levels were of the order of 200 to 230 mm. Hg, became pressor when blood pressure was reduced to about 160 mm. Hg by carbon dioxide. But when the carbon dioxide concentration reached 50 per cent, refractoriness developed as in normal animals. In some neurogenic hypertensive dogs, pressure fell 180 mm. Hg or more and remained depressed a few minutes. Pressure was so low and heart beat so slow, we despaired of their lives. (Preliminary atropinization often avoids this depression.) Then pressure spontaneously rose to control value or even above, despite maintenance of blood pH values around 6.80. Administration of pressor or depressor drugs demonstrated that refractoriness had developed.

Thus, the chain of autonomic ganglions in the neurogenic hypertensive dog is apparently the means of developing refractoriness, as it is in normal and renal hypertensive animals. Only in sympathectomized dogs is the means not present; hence refractoriness does not develop.

We found that tetraethylammonium chloride, like carbon dioxide, produces great depressor response in neurogenic hypertensive dogs, but differs in sympathectomized dogs by usually producing a pressor response. Perhaps the tetraethylammonium depressor response is due to blockade of sympathetic impulses which might be partially responsible for continued hypertension. In sympathectomized dogs, absence of ganglions and presence of normal pressure levels do not provide conditions for the powerful depressor action of tetraethylammonium.

If carbon dioxide produces an exaggerated depressor response in sympathectomized dogs because of supersensitivity at the myoneural junction created by the denervation, and resection of carotid sinuses and vagus nerves in acute studies fails to elicit such supersensitivity, how do we explain the exaggerated depressor response to carbon dioxide in neurogenic hypertensive animals?

That carbon dioxide materially slows the heart, even after thorough atropinization, is certainly one factor. Secondly, that electrical stimulation of the sympathetic chain elicits hypertension characterized by abnormal hypotensive response to carbon dioxide suggests that in neurogenic hypertensives increased sympathetic vasoconstrictor activity likewise has had a part in such hypertension. These two factors appear to account for the supernormal depressor response of the neurogenic hypertensive.

Could these events occur under less drastic circumstances? In these experiments, curare abolishes the animal's defense against composition changes of the inspired gas mixture, leaving tissues subject to Henry's law. But exposure to abnormal gas seldom exceeded a half hour, and was usually less. When lower concentrations of carbon dioxide were inhaled an hour or more, much the same phenomena occurred as with higher concentrations for shorter periods.

During periods of sluggish circulation, as in shock, congestive heart failure, myocardial infarction, coma and during anesthesia, especially when respiratory defenses are at a low ebb, the partial pressure of carbon dioxide may attain high values and elicit vascular refractoriness. We have shown that refractoriness occurs in shock and cardiac failure.[1] Under less trying clinical conditions, small changes in carbon dioxide content of blood may affect sympathetic ganglions to increase or decrease vascular responsiveness without eliciting the extreme refractoriness we sought in these studies. When it is realized that the heart muscle and the blood vessels are similarly responsive, changes in reactivity become more important than if they were limited to specialized vascular beds.

Our use of curare was fortunate, because by blocking responses of the respiratory center, certain fundamental aspects of the circulatory

effects of carbon dioxide were uncovered. The availability of respiratory compensatory mechanisms normally prevents just the sort of changes we have described from becoming manifest.

Summary

1. Under pentobarbital and curare, dogs given carbon dioxide–oxygen mixtures showed transitory hypotension with bradycardia, usually followed by a rise of pressure to or above control levels. At high carbon dioxide concentrations, hypotension was usually persistent. Vagotomy, atropine, resection of carotid sinuses, or both, failed to affect the response. Bilateral ganglionectomy from T1 to T9 nearly doubled the depressor response. Cardiac denervation may have increased it slightly; it was further increased by "total" sympathectomy. Animals with spinal cord destruction from C6 caudad responded similarly to sympathectomized dogs. Tetraethylammonium chloride in doses sufficient to block autonomic ganglionic transmission did not significantly modify the initial hypotensive effect of carbon dioxide. The depressor action of carbon dioxide is not histaminergic since it is not altered by Benadryl.

2. A failure of arterial pressure to respond to pressor and depressor agents (vascular refractoriness) was elicited in normal dogs by inhalation of carbon dioxide–oxygen mixtures. The speed of onset of refractoriness varied with the concentration of carbon dioxide administered. Refractoriness often disappeared within a few minutes after restoration of the animal to atmospheric air. Adrenaline responses were most easily abolished, noradrenaline less so and angiotonin and barium chloride, least. Drugs such as sodium azide, sodium nitroprusside, and partially purified veratrum alkaloids showed greatly reduced depressor activities. Gas mixtures high in nitrogen, even to the point of asphyxia, failed to elicit the phenomena characteristic of carbon dioxide–oxygen inhalation.

3. Tetraethylammonium chloride given during a period of refractoriness, usually caused a large rise in arterial pressure, often followed by a fall. Responsiveness was partially restored; complete recovery, only when carbon dioxide was discontinued.

4. Carotid sinus resection, vagotomy, adrenalectomy, thorough atropinization and section of spinal cord at C6 did not significantly influence development of refractoriness; preliminary autonomic ganglionic blockade with tetraethylammonium chloride gave partial protection against it. "Total" surgical sympathectomy alone entirely prevented its appearance.

5. Experiments in which the head of a dog, connected to its body only by the nervous system, was perfused by a donor dog, showed that the recipient's body remained reactive when refractoriness had been established in the donor dog by carbon dioxide–oxygen inhalation. Administration of the gas mixture to the recipient's body quickly elicited the refractory state. Neither asphyxia of the recipient's brain by reducing its blood supply nor asphyxia of the donor animal altered the recipient's responses.

6. Blood pH fell to the same low levels in sympathectomized as in normal animals; yet in the former reactivity was maintained and in the latter lost. Reappearance of reactivity following tetraethylammonium administration was not accompanied by rise in pH toward normal. Infusions of hydrochloric or lactic acids failed to elicit the low pH caused by carbon dioxide and did not reproduce the vascular phenomena characteristic of carbon dioxide inhalation.

7. Dogs with experimental renal hypertension responded normally to most vasoactive substances tested. Sodium nitroprusside and 30 per cent carbon dioxide gave slightly abnormal depressor responses. Neurogenic hypertensive animals showed greatly augmented depressor responses to carbon dioxide, azide, and nitroprusside, and very slightly reduced pressor responses to adrenaline and noradrenaline.

8. Refractoriness developed in renal hypertensive just as in normal animals. The sequence was somewhat different in neurogenic hypertensives in which at lower concentrations of

carbon dioxide, responsiveness usually increased; at higher concentrations, responsiveness became inhibited. Changes in blood pH were roughly the same for all groups.

9. "Totally" sympathectomized animals were even more sensitive than neurogenic hypertensives to the hypotensive action of carbon dioxide; in contrast with neurogenic and renal hypertensives they failed to develop refractoriness.

Conclusions

Carbon dioxide produces hypotension and severe vascular refractoriness in dogs under pentobarbital-curare: the onset of refractoriness is partially inhibited by autonomic ganglionic blockade and completely prevented by total sympathectomy. The stimuli acting on the vascular musculature to elicit refractoriness originate from direct action of carbon dioxide on sympathetic ganglions and, in acute experiments, are independent of central nervous regulation.

Animals with experimental renal hypertension react normally to carbon dioxide and several other vasoactive substances. Neurogenic hypertensives, contrariwise, exhibit greatly augmented depressor responses. Both experimental groups develop vascular refractoriness under carbon dioxide. In contrast, totally sympathectomized dogs do not develop refractoriness. Their concurrent sensitivity to the hypotensive action of carbon dioxide is exquisite and is due to absence of autonomic ganglions on the one hand and to failure of the buffer mechanism on the other. The onset of vascular refractoriness is thus dissociated from the presence of hypotension. It is also independent of changes in blood pH.

Heightened vasoconstrictor tone in experimental renal hypertension does not appear to be attributable to greatly increased vasomotor activity as it is in experimental neurogenic hypertension.

References

[1] Page, I. H.: Cardiovascular changes resulting from severe scalds. Am. J. Physiol. **142:** 366, 1942.

[2] Guyton, A. C., and Reeder, R. C.: Quantitative studies in the autonomic actions of curare. J. Pharmacol. & Exper. Therap. **98:** 188, 1950.

[3] Pauling, L., Wood, R. E., and Sturdivant, C. O.: An instrument for determining the partial pressure of O_2 in a gas. Science, **103:** 338, 1946.

[4] Claff, C. L.: Glass electrode for determination of hydrogen ion activity of small quantities of culture media. Science **94:** 285, 1941.

[5] Van Slyke, D. D., and Neill, J. M.: The determination of gases in blood and other solutions by vacuum extraction and manometric measurement. J. Biol. Chem. **61:** 523, 1924.

[6] Brinkman, W. S.: Determination and continuous registration of the percentage oxygen saturation in clinical conditions. Arch. chir. Neerl. **1:** 177, 1949.

[7] Page, I. H.: A method for producing persistent hypertension by cellophane. Science **89:** 273, 1939.

[8] —, and Taylor, R. D.: Variations of vascular reactivity in normal and hypertensive dogs. Am. J. Physiol. **156:** 412, 1949.

[9] Dautrebande, L.: Réactions vaso-motrices à l'oxygène et à l'acide carbonique chez le chien en hypertension artérielle par énervation des zones vasosensibles. Arch. internat. de pharmacodyn. et de ther. **40:** 107, 1931.

[10] Gellhorn, E.: Autonomic Regulations: Their Significance for Physiology, Psychology and Neuropsychiatry. New York, Interscience, 1943.

[11] Cannon, W. B., Lewis, J. T., and Britton, S. W.: Studies on the conditions of activity in endocrine glands. XVII. A lasting preparation of the denervated heart for detecting internal secretions, with evidence for accessory accelerator fibers from the thoracic sympathetic chain. Am. J. Physiol. **77:** 326, 1927.

[12] Taylor, R. D., and Page, I. H.: In preparation.

[13] Miller, F. A., Brown, E. B., and Varco, R. L.: Certain effects in dogs of inspiring 15–30 per cent carbon dioxide. Federation Proc. **9:** 89, 1950.

[14] Koppanyi, T., and Vivino, A. E.: Dimethylpiperidines as primary ganglionic depressants. Federation Proc. **5:** 186, 1946.

[15] Bacq, Z. M., Brouha, L., and Heymans, C.: Section des nerfs aortiques et sinocarotidius chez le chien totalement sympathectomisé. Quelques comparaisons entre le chien et la chat sympathectomisés. Compt. rend. Soc. de biol. **115:** 1380, 1934.

[16] Wiggers, C. J.: A study of the direct effect of hypercapnia on the contraction of the mammalian ventricle. Am. J. Physiol. **90:** 230, 1929.

[17] Page, I. H., and Taylor, R. D.: Augmentation of vasoactive substances by tetraethylammonium chloride. Circulation **1:** 1233, 1950.

[18] Schmidt, C. F., and Pierson, J. C.: The intrinsic regulation of the blood vessels of the medulla oblongata. Am. J. Physiol. **108:** 241, 1934.

[19] Fleisch, A., Sibul, I., and Ponomarev, P.: Über die nutritive Kreislaufregulierung. I. Kohlensäure und säuerstoffmangel als auslosende Reize. Arch. f. d. ges. Physiol. **230:** 814, 1932.

[20] Acheson, G. H., and Moe, G. K.: The action of tetraethylammonium ion on the mammalian circulation. J. Pharmacol. & Exper. Therap. **87:** 220, 1946.

[21] Burget, G. E., and Visscher, M. B.: Variations of the pH of the blood and the response of the vascular system to adrenalin. Am. J. Physiol. **81:** 113, 1927.

[22] Stavraky, G. W.: The effect of pulmonary ventilation on the pressor action of adrenaline. Am. J. Physiol. **137:** 485, 1942.

The Effect of Priscoline on Peripheral Blood Flow in Normal Subjects and Patients with Peripheral Vascular Disorders

By THEODORE B. VAN ITALLIE, M.D., AND CHARLES W. CLARKE, JR., M.D.

Using the venous occlusion plethysmograph the authors have studied the peripheral circulation of normal subjects and persons with peripheral vascular disease. It is demonstrated that the vasodilating agent Priscoline (2-benzyl-4,5-imidazoline hydrochloride) frequently increases peripheral blood flow to a degree comparable to that produced by either sympathectomy or indirect body heating. In addition, the combined use of plethysmography and a vasodilating procedure is shown to be of value in the diagnosis of peripheral vascular disorders.

IN A RECENT review of clinical plethysmography,[1] Goetz states that immersion of an extremity for 30 minutes in a tank of water kept at 45 C., with the subject covered by blankets to prevent loss of body heat, is still the method of choice for relaxing central vasomotor tone. Previously, he had affirmed that this particular technic (adapted from Gibbon and Landis[2]) was ordinarily comparable in its effects to spinal anesthesia and paravertebral block. From the study of a large series of cases, Goetz found that by body heating he was able to distinguish between the vasospastic and the organic components of peripheral arterial disease, and to estimate the extent of each. In the presence of an arterial block, he was able to measure the degree of collateral circulation by the venous occlusion method. By use of plethysmography in conjunction with the body-heating procedure, he was able to predict and evaluate the effects of lumbar sympathectomy.

On the basis of the work of Goetz and his associates, it appeared that their method of body heating might prove to be a useful yardstick against which to measure the effect of certain vasodilating drugs. Accordingly, an experiment was devised whereby the effect of Priscoline (2-benzyl-4,5-imidazoline hydrochloride), a widely used vasodilating drug, could be compared to the effect of body heating on the peripheral blood flow in normal individuals and in patients suffering from various degrees of peripheral arterial insufficiency.

The pharmacology of Priscoline has been reviewed by a number of authors.[3-5] Its pharmacologic effects are manifold. Its effect on cardiac output is variable.[6] In larger doses, it acts as an adrenergic blocking agent; in the smaller commonly used doses, it is said to be an effective local vasodilator, particularly in the skin of the extremities.

PROCEDURE

Five normal individuals and 23 patients with complaints suggesting peripheral arterial insufficiency were studied. Each subject visited the laboratory on at least two occasions, separated by an interval of a day or more. In no instance was the subject permitted to smoke, to drink liquor, tea or coffee, or to consume a heavy meal within the 12 hour period preceding the visits.

Upon arrival, the subject was given a hospital garment to wear. He was then asked to lie upon a bed which was kept at a fixed gatch throughout the investigation. The trunk was elevated at an angle of 40 degrees and the knees were slightly raised. An attempt was made to prevent drafts and sudden distracting noises.

Skin temperatures were measured at previously marked points on the trunk, arms and hands, legs and feet, by means of a McKesson Dermalor Thermocouple. Oscillometric readings were taken at the wrists and ankles, and in some instances at the calves and thighs, with a Collens Sphygmo-Oscillometer. The blood pressure and oral temperature were recorded by clinical methods.

Plastic plethysmograph cups were then placed

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upon a toe (usually the great toe) of each foot. In subjects who gave no clinical evidence suggesting an appreciable difference in blood flow in the two lower extremities, one of the cups was attached to the index finger of the left hand. The material used to produce an airtight seal between the cup and the skin without jeopardizing venous drainage was Cambridge Plethysmograph Jelly, a plastic mixture of printer's roller compound and glue.

The subject was kept comfortable at bed rest for a period of 45 to 90 minutes. Then, by use of an air reservoir, blood pressure cuffs placed at the ankles or at the ankle and wrist were rapidly inflated to a pressure level of 42 to 46 mm. Hg. The pulse volumes prior to venous occlusion and the blood flow on venous occlusion were recorded from both parts simultaneously on a plethysmokymograph.

The plethysmokymograph used in this study was constructed on the basis of a principle described in detail by Goetz in 1940.[7] It consists of two horizontal 1 cc. volumetric pipets of identical bore mounted side by side on an optical bench. In each pipet is a small column of alcohol. The plethysmograph cups attached to the digits are connected with the pipets by means of thick-walled capillary rubber tubing. In the airtight system, in which the air content is at a minimum, the alcohol columns in the pipets are activated by changes in volume of the enclosed digits. The pulsating columns cast moving shadows in the optical field which are projected to the photographic paper in a photokymograph. In this instance, the photokymograph is an electrocardiograph camera. A clock timer permits the accurate measurement of paper speed, and a pneumograph attachment makes possible the recording of the respiratory excursions. Since the pipets are already calibrated, the calibration is optically projected to the photographic paper and recorded along with the shadows produced by the pulsating meniscuses.

The mounting of the various lenses and the pipets on an optical bench makes it possible to alter the size of the image as desired. Changes in volume of 0.001 cc. are readily distinguished in the completed plethysmogram. The recording of digital pulsations and rate of congestion on venous occlusion in two parts simultaneously permits an exact comparison of the vascular status in two extremities. An example of this may be found in figure 1 *C*. The tracings in *C* are taken from the two great toes of a patient (G. L.) with thromboangiitis obliterans involving both lower extremities. No pulsations are visible from the left side, suggesting complete occlusion of a major vessel in that extremity. The rate of increase of digital volume following venous occlusion is presumed in this instance to be a measure of the collateral circulation. The difference between the two sides is readily appreciated.

The blood flow measurements taken after completion of the rest period were ordinarily repeated at least twice. If found consistent, they were regarded as the "resting levels." When the resting levels for blood flow and pulse volume had been recorded, 50 mg. of Priscoline was administered to the subject intramuscularly. Pulse volumes and blood flow were recorded 5, 10, 20 and 30 minutes after the administration of the drug. Thirty-five minutes after the Priscoline had been given the oral temperature, blood pressure, skin temperatures and oscillometric readings were again recorded. The volumes of the enclosed digits were measured. In the case of the toe, this was done by making a mould of the enclosed portion with plasticene. The internal volume of the mould was then measured by

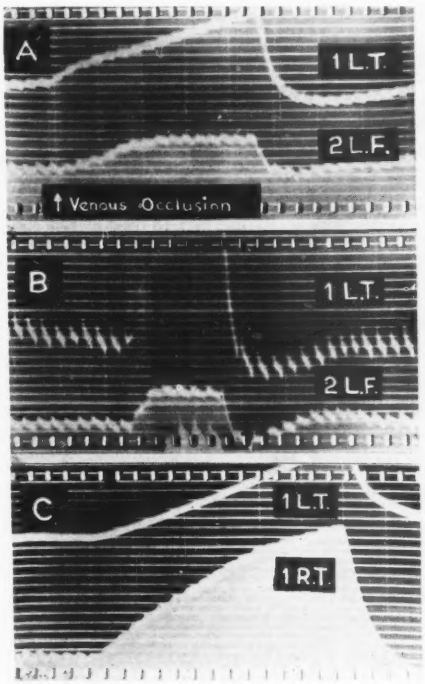

FIG. 1. Representative Plethysmograms. (Venous occlusion at arrow. White horizontal lines indicate changes in volume of 0.01 cc. Ordinates equal 3 seconds. From the rate of increase of digital volume after venous occlusion (slope of curve) the values for blood flow can be calculated. From the amplitude of pulsations, pulse volume is calculated. Details in text: *A*. Normal subject at rest (first left toe and second left finger). *B*. Same subject ten minutes after intramuscular injection of 50 mg. of Priscoline. *C*. Subject with thromboangiitis obliterans involving both lower extremities (first left toe and first right toe). Tracing recorded 20 minutes after indirect body heating. Note complete absence of pulsations on the left.

filling it with water from a pipet. The finger volume was measured by observing the amount of water it displaced from a graduated cylinder.

In order to standardize the results, it was necessary to correct for variations in digital volume. This was done by correcting the digital volumes to a mean of 15 cc. The corrected pulse volume and rates of blood flow* were calculated by use of two formulas[8]:

$$\frac{\textit{pulse volume}}{\textit{(corrected)}} = \frac{\textit{pulse volume (recorded)} \times 15}{\textit{digital volume in cc.}} \quad (1)$$

$$r = k\frac{i \times 100 \times 60}{v} \quad (2)$$

where r is the rate of blood flow in cc. per minute per 100 cc. of tissue; k is a constant to correct for the site of the occluding cuff (it is 3 at the wrist[8-9] and ankle); i is the increase in digital volume per second in cc.; v is the digital volume in cc.

On the second visit, similar observations were made with regard to resting values for blood flow and pulse volume. The skin temperatures, oscillometric readings, blood pressure and oral temperature were also recorded as before. Then the subject's right arm was immersed to a point 4 to 6 inches above the elbow in water kept at 40–47 C. The subject was covered by a woolen blanket to prevent dissipation of heat.

Blood flow and pulse volume were measured 10, 20 and 30 minutes after immersion of the arm. Fifteen of the subjects received 50 mg. of Priscoline 35 minutes after the start of body heating, and pulse volume and blood flow were measured, 5, 10 and 20 minutes thereafter. Except for the use of the heating technic instead of Priscoline, the conditions of the two experimental periods were kept as nearly similar as possible.

Results

For the purpose of evaluating the results clinically, the subjects were divided into four groups: normal individuals; patients with vasospastic disease; patients with organic disease; sympathectomized patients.

Normal subjects, in this investigation, were volunteers below the age of 30, without complaints or symptoms referable to the circulatory system, and in whom there was no clinical evidence of peripheral vascular disease.

The group with vasospastic disease included those patients who gave evidence of peripheral arterial insufficiency, but in whom body heating could produce pulse volume and blood flow values well in excess of those found under similar conditions in the group with organic disease. This group had resting values which tended to be considerably lower than normal and which, in the absence of a successful vasodilating procedure, could well have been interpreted as evidence of organic occlusive disease. They described symptoms such as cold extremities, nocturnal leg pains, and intermittent claudication. These patients especially displayed marked improvement on oral Priscoline (25 to 50 mg. four times a day). This group included 2 men and 2 women. One subject (G. L.) had had a unilateral sympathectomy. Their ages ranged from 29 to 51.

The group with organic disease was made up of patients who had unmistakable clinical evidence of peripheral arterial insufficiency and who, during plethysmography, displayed impaired digital blood flow and pulse volume after body heating. There were 15 subjects in the organic disease series. This group was the largest and also the oldest studied. The average age of its members was 63 years. They ranged in age from 40 to 86. There were 11 men and 4 women.

The remaining group consisted of 3 individuals who had undergone unilateral lumbar sympathectomy for the relief of symptoms of arterial insufficiency.

The essential data,* including skin temperature readings, with respect to the 5 normal volunteer subjects and the 23 patients studied are in table 1.

Prior to the administration of Priscoline, the average resting blood flow of the 5 normal persons was found to be 12.6 cc. (per minute per 100 cc. of tissue). The group of patients with vasospastic disease had a resting blood flow which averaged 2.4 cc., illustrating the

* Approximate blood flow values (after indirect body heating): normal, 45–100 cc./min./100 cc. tissue; borderline, 35–45 cc./min./100 cc. tissue; pathologic, <35 cc./min./100 cc. tissue.

Approximate pulse volume values: normal, >0.175 cc.; borderline, 0.0125–0.0175 cc.; pathologic, <0.0125 cc.

* Data derived from oral temperature and blood pressure studies and the oscillometric readings and skin temperature determinations were analyzed. However, the complete findings are not presented in detail in this paper because of limitations in space. They will be discussed in a separate communication.

markedly impaired flow which can be found in this type of disorder. The average resting blood flow in the group with organic disease was 1[illegible].5 cc. The averages for pulse volume at rest in the three groups were respectively 0.006 c[illegible]., 0.0018 cc. and 0.0025 cc. Following the administration of Priscoline, the averages for maximal blood flow were as follows: normal group, 56.6 cc.; vasospastic disease group, 25.8 cc.; organic disease group, 22.9 cc. Thus, in the normal group, blood flow increased approximately fivefold; for the patients with vasospastic disease the increase was approximately tenfold. In the group with organic disease, the blood flow was only doubled. The averages for pulse volume in the three groups were calculated to be 0.0178 cc., 0.0144 cc. and 0.0034 cc. respectively. This represented a threefold increase in the normal group, an eightfold increase in the vasospastic group, and less than a twofold increase in the group with organic disease.

Average resting values for blood flow in the three groups prior to body heating were: normal group, 29.4 cc.; vasospastic disease group, 5.8 cc.; and organic disease group, 12.3 cc. After body heating these averages increased to 79.2 cc., 49.8 cc. and 21.1 cc. respectively. The increases exhibited were thus approximately threefold for normal patients, ninefold for patients with vasospastic disease, and, again, less than twofold for patients with organic disease.

The average values for resting pulse volume prior to heating were: normal group, 0.009 cc.; vasospastic group, 0.0056 cc., and organic group, 0.0014 cc. These values increased to 0.017 cc., 0.019 cc. and 0.003 cc. respectively, after heating. Increases, therefore, were approximately twofold in the group of normal patients, threefold among those with vasospastic disease, and twofold in the group of patients with organic disease.

After indirect body heating followed by the administration of Priscoline, the averages for blood flow among the various groups studied were as follows: normal group, 48 cc., vasospastic group 75.3 cc., and organic group, 25 cc. Using the average resting values found prior to body heating (29.4 cc., 5.8 cc., and 12.3 cc.) the increases proved to be less than twofold in the one normal subject studied,* approximately thirteenfold for patients with vasospastic disorders, and twofold for those with organic disorders.

Average pulse volumes after heat followed by Priscoline administration were 0.011 cc., 0.021 cc. and 0.0048 cc. for normal subjects, the vasospastic disease group and the organic disease group respectively. Using the resting values obtained prior to body heating (0.009 cc., 0.0056 cc., 0.0014 cc.) as a base, the increases were fourfold in the group with vasospastic disease and threefold in the group with organic peripheral vascular disease. The one "normal" subject studied in this manner is not representative of normal subjects (see earlier footnote).

In order to emphasize their distinguishing characteristics, the averages derived from each group are shown together graphically in figure 2.

Under separate consideration is the group of patients studied before and after sympathectomy. Prior to operation, these subjects showed an average resting blood flow of 15 cc. which rose to 18 cc. after Priscoline. The pulse volume remained at 0.001 cc. After sympathectomy the average resting blood flow was 24 cc., increasing to 31 cc. after Priscoline. Following the administration of Priscoline, the average pulse volume increased from 0.003 cc. to 0.008 cc. among postsympathectomy patients.

The average resting blood flow prior to body heating in patients before operation was 18 cc. After heating, the average blood flow was 25 cc., and after heat plus Priscoline it increased to 30 cc. Pulse volumes remained at 0.000 cc. during these tests.

After sympathectomy, the average resting blood flow was 25 cc. before heating, 23 cc. after heating and 24 cc. after heating plus

* Poor pulse volume and blood flow increases noted here are based on study of a single patient in the normal group. Subsequent studies have shown this to be in error, as most normal persons will respond with greatly increased (four- or sixfold) blood flow and pulse volume when heat and Priscoline are administered together.

TABLE 1.—*Data Obtained by Plethysmographic and Skin Temperature Studies of Normal Persons, Patients with Vasospastic and Organic Peripheral Vascular Diseases and Certain Patients before and after Sympathectomy. The Instruments and Technics Used are Described in the Text.*

Patient and Diagnosis	Age	Resting Values before Priscoline		Maximal Values after Priscoline		Resting Values before Heating		Maximal Values after Heating		Maximal Values after Heating Plus Priscoline		Leg and Foot Temperatures (°C.)			
		Blood Flow†	Pulse Volume‡	Blood Flow	Pulse Volume	Blood Flow	Pulse Volume	Blood Flow	Pulse Volume	Blood Flow	Pulse Volume	Before Priscoline	After Priscoline	Before Heat or Heat + Priscoline	After Heat or Heat + Priscoline
Normal Group															
B. P.♀ Normal	21	10	.004	83	.019	37	.01	87	.021	—	—	30.8/30.0	30.1/32.0	32.0/30.4	31.2/32
D. M.♀ Normal	22	8	.005	41	.019	9	.007	56	.012	—	—	33.6/33.6	33.8/34.6	32.3/32.3	34.8/34.5
P. J.♀ Normal	22	8	.007	56	.019	64	.014	120	.023	—	—	33.6/33.6	33.8/34.6	33/35	35/35
H. R.♀ Normal	23	30	.011	75	.019	30	.011	93	.019	—	—	34.2/32.8	34.8/33.4	34.2/31.8	33.7/33.9
N. G.♀ Normal	26	7	.003	28	.013	7	.003	40	.01	48	.011	31.0/27	31.8/30.4	28.5/28.0	32.0/34.3
Average		12.6	.006	56.6	.0178	29.4	.009	79.2	.017	48	.011				
Vasospastic Group															
H. F.♂? Thromboangiitis Obliterans	51	3	.004	27	.009	1	.004	36	.011	45	.013	31.2/27.4	29.2/29.8	29.5/24.2	30/31.4
A. H.♀ Cold Extremities, Pain in Calves (lt. toe)	31	2	.001	17	.015	11	.010	34	.020	—	—	33/31	32.5/29.5	30.4/28.9	32.7/33.4
A. H. (rt. toe)		2	.001	13	.015	11	.010	52	.025	—	—	32.9/31.5	32.3/29.3	31.8/26.7	33.2/33.3
R. J.♀ Raynaud's Disease	29	4	.002	44	.020	5	.003	72	.020	96	.025	31/30.9	30.2/34	32.2/31.4	32.2/35.3
G. L.♂ Thromboangiitis Obliterans (rt. toe)	40	1	.001	28	.013	1	.001	55	.019	85	.025	31/28.8	31/31.8	30.2/32.2	31.4/33.2
Average		2.4	.0018	25.8	.0144	5.8	.0056	49.8	.019	75.33	.021				
Organic Group															
L. F.♀ Arteriosclerotic Peripheral Vascular Disease (rt. toe)	67	4	.001	16	.001	15	.001	26	.002	26	.002	31/29.8	30.6/31.8	31.7/33.2	32.3/33.8
L. F. (lt. toe)		6	.000	9	.000	8	.000	11	.001	4*	.001	30.6/29.2	30.4/29.4	32.6/32.3	33.4/31.8
A. W.♂ Arteriosclerotic Peripheral Vascular Disease (rt. toe)	71	14	.000	12*	.000	7	.000	16	.000	12*	.000	31.1/29.4	30.7/30.9	31/28.4	31.2/30
A. W. (lt. toe)		9	.000	12	.000	10	.000	7*	.000	7*	.000	32.5/28.2	31.5/28.1	32/29.8	30.2/29.2
B. N.♀ Arteriosclerotic Peripheral Vascular Disease	81	15	.000	39	.001	9	.000	26	.001	—	—	30.8/31.6	31.0/33.1	31.8/31.8	32.9/34.5

W. F.♂ Arteriosclerotic Peripheral Vascular Disease. (Diabetes)	62	22	.003	25	.007	22	.003	33	.007	—	—	32.4/33.2	32.9/33.6	30.4/31.4	32/32.8
G. G.♂ Arteriosclerotic Peripheral Vascular Disease	68	18	.001	35	.001	28	.001	34	.001	34	.001	33.2/28.8	31.1/31.3	—	—
J. H.♂ Arteriosclerotic Peripheral Vascular Disease (Diabetes)	86	14	.001	20	.001	13	.001	16	.001	18	.001	31.0/29.8	32.2/28.8	32.8/28.6	33.3/29.8
E. E.♂ Arteriosclerotic Peripheral Vascular Disease (lt. toe)	74	81	.001	21	.002	19	.001	27	.002	30	.002	32/26.6	31.7/29	28.5/25.6	31.7/28.7
E. E. (rt. toe)		18	.004	33	.006	6	.002	18	.002	24	.004	29/31	30.8/32.7	29/28.1	31.4/31.7
M. K.♀ Scleroderma	51	6	.001	33	.014	6	.001	14	.001	38	.014	31.6/30	31.2/31.8	33.5/29	35.3/35.1
J. O'C.♂ Arteriosclerotic Peripheral Vascular Disease	62	17	.002	27	.009	7	.007	33	.009	51	.012	30.1/27	32.0/31.8	32.7/28.8	33.1/33.3
E. McS.♂ Thromboangiitis Obliterans	40	2	.000	8	.000	8	.000	27	.001	—	—	30.6/26	29.2/26.9	31.5/31	31.4/29
T. B.♂ Arteriosclerotic Peripheral Vascular Disease. (Diabetes) (rt. toe)	55	1	.001	10	.006	1	.001	20	.013	35	.019	31.8/26.4	30.4/27.8	33/28.7	34.8/32.9
T. B. (lt. toe)		1	.001	8	.006	1	.001	10	.006	25	.013	32.8/27.6	30.6/28.8	34/29.2	34.5/33.4
C. S.(a)♂ Arteriosclerotic Peripheral Vascular Disease. (Diabetes).	65	8	.001	13	.001	6	.001	14	.002	16	.003	31.4/29.9	31.4/31.4	29.1/26.8	29.1/28.7
M. H.♀ Arteriosclerotic Peripheral Vascular Disease. (Diabetes).	76	12	.002	24	.002	15	.002	17	.002	11*	.001	31.6/28.2	30.2/31.2	32/31.2	31.2/30.9
G. L.♂ Thromboangiitis Obliterans (lt. toe)	40	18	.000	25	.000	18	.000	28	.000	30	.000	32.8/28	32.5/32.4	32.4/29.6	32.7/32.9
G. L. (rt. toe)		13	.004	28	.008	13	.004	15	.005	20	.005	32/28.1	34.2/30.8	31/29.6	33.8/33.4
C. S.(b)♂ Arteriosclerotic Peripheral Vascular Disease.	52	14	.002	60	.004	34	.002	30	.004	44	.004	32.4/30	30.8/32.2	31.1/28.5	30.0/32.8
Average		11.5	.0025	22.9	.00345	12.3	.0014	21.1	.003	25	.0048				

† Blood flow is measured in cc./min./100 cc. of tissue.

‡ Pulse volume is measured in cc.

* Blood flow decreased to this level.

The instruments and technic used are described in the text.

TABLE 1—*Continued*

Patient and Diagnosis	Age	Resting Values before Priscoline		Maximal Values after Priscoline		Resting Values before Heating		Maximal Values after Heating		Maximal Values after Heating Plus Priscoline		Leg and Foot Temperatures (°C.)			
		Blood Flow†	Pulse Volume‡	Blood Flow	Pulse Volume	Blood Flow	Pulse Volume	Blood Flow	Pulse Volume	Blood Flow	Pulse Volume	Before	After	Before	After
												Priscoline		Heat or Heat + Priscoline	
Pre and Postsympathectomy Group															
G. L.♂ Thromboangiitis Obliterans (Presympathectomy)	40	18	.000	25	.000	18	.000	25	.000	30	.000	32.8/28	32.5/32.4	32.4/29.6	32.7/32.9
G. L. (Postsympathectomy)		33	.001	40	.005	33	.004	30*	.004	35	.004	31.6/32.4	32.3/32.6	32.2/32	33.2/34.2
W. F.♂ Arteriosclerotic Peripheral Vascular Disease. (Diabetes). (Presympathectomy)	35	11	.001	11	.001	—	—	—	—	—	—	—	—	—	—
W. F. (Postsympathectomy)		15	.001	19	.009	19	.004	17*	.005	13*	.005	31/30.4	31/30.8	31.9/31.8	32.1/31.8
L. G.♂ Arteriosclerotic Peripheral Vascular Disease (Postsympathectomy)	35	24	.008	34	.009	24	.008	21*	.009	—	—	30.2/32.2	29.4/31.4	31.4/32	33/32.5
Average (Presympathectomy)		15	.001	18	.001	18	.000	25	.000	30	.000				
Average (Postsympathectomy)		24	.003	31	.008	25	.005	23	.006	24	.005				

† Blood flow is measured in cc./min./100 cc. of tissue.
‡ Pulse volume is measured in cc.
* Blood flow decreased to this level.
The instruments and technic used are described in the text.

Priscoline. The average postoperative pulse volume before heating was 0.005 cc., after heat 0.006 cc. and after heat followed by Priscoline 0.005 cc.

The averages derived from the pre- and postsympathectomy groups also appear in figure 2.

No serious toxic effects were observed following the intramuscular administration of Priscoline* to the 28 patients studied, with one exception. This occurred in an 83 year old woman with arteriosclerotic peripheral vascular disease, who fainted as she changed from the supine to a standing position. A concomitant fall in blood pressure could not be measured. Formication and piloerection were reported by 12 patients, a feeling of warmth occurred in 9, flushing in 6, chilly sensations in 5, palpitation and tachycardia in 4 and diaphoresis and nausea in 2 cases.

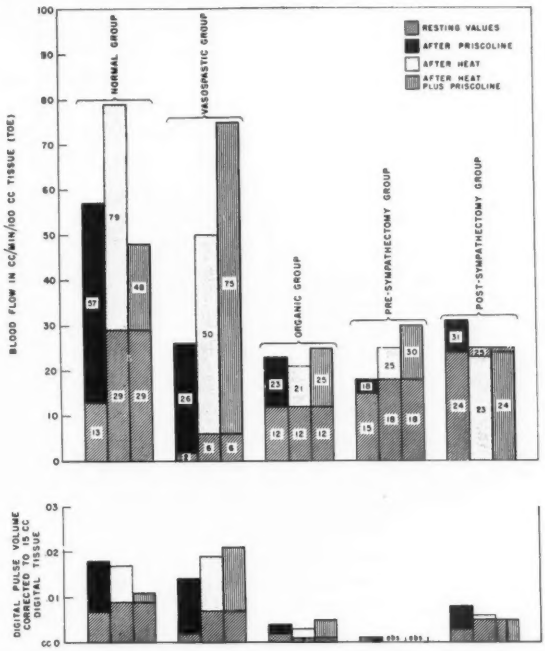

FIG. 2. Averages of results obtained by plethysmographic study of the four groups examined (normal, vasospastic, organic, pre- and postsympathectomy). Poor blood flow shown above in normal group after administration of heat plus Priscoline is not in agreement with more recently recorded results (unpublished).

COMMENT

In brief, the lowest resting values are found among patients with vasospastic diseases, yet these same individuals exhibit the greatest increase in blood flow after body heating and/or Priscoline. In contrast, postsympathectomy patients, being already more or less in full vasodilatation, show the least increase in blood flow after heat or Priscoline, and nearly the highest resting values. Also it is seen that while the average patient with organic peripheral vascular disease displays a value for resting blood flow below that found in a normal person, the presence of permanent changes in the arteries and arterioles is best demonstrated by their inability to dilate in response to Priscoline or heat and thereby produce increases in blood flow to the degree observed in normal persons. It is also seen that body heating and Priscoline are roughly comparable in their effects on blood flow.

It is well to state that the Goetz modification

* All patients received 50 mg. with the exception of 2 of small stature who received 37 mg.

of the Gibbon and Landis procedure for ablating sympathetic tone, although useful, is not invariably effective. Goetz, in his writings, has pointed out several qualifications. First, there are certain rare individuals whose sympathetic tone simply cannot be relaxed by the procedure of body heating. Such individuals, says Goetz, respond well to the direct application of heat. Second, patients suffering vascular impairment of the immersed extremity will have a poor return to the hypothalamus of heated blood.[10] Accordingly, vasorelaxation will be delayed, diminished, or absent, depending on the heat gradient influencing the hypothalamus.

In spite of these qualifications, it appears that the diagnostic use of body heating by the indirect method has satisfactorily stood the test of clinical application and may be regarded as a useful standard against which the effect of Priscoline and other vasodilating drugs can be measured. Body heating by the indirect method is a practical and safe procedure, and therefore well adapted to investigations involving studies on patients.

An examination of the resting values for each group makes it plain that little of diagnostic value is to be gained from a study of resting values alone. However, in unpublished studies done in this laboratory it was shown that in normal subjects, Priscoline had an effect on resting blood flow and pulse volume in the toes that was about three times as great as the effect on the resting values in the fingers at the same time. It was further found that the average resting blood flow and pulse volume values in the digits of the lower extremity in this group was approximately one-third that found in the digits of the upper extremity. This finding was consistent with what is already known about the arterial and arteriolar tone in the lower extremities, namely, that the tone there considerably exceeds that found in the fingers. This has been regarded by some authors as an adaptation on the part of the circulation to the increased arterial pressure and flow produced in the legs by the upright posture of the human body. In any case, this normally increased tone in the lower extremities should not be confused with "spasm."

The fact, then, that a greater response is elicited in the toes by Priscoline than in the fingers, is hardly a basis for believing that the vasculature of the skin of the toes is unusually responsive to the drug in a pharmacologic sense. The more feasible and, indeed, obvious explanation is that the toes' vessels are more constricted at the outset and therefore are capable of a wider range of dilatation.

In some instances, Priscoline was able to produce a rather marked increase in blood flow over resting values when body heating did not. This was true even if the resting values were similar. The administration of Priscoline to patients already subjected to prolonged body heating produced variable results. In certain individuals with severe organic peripheral vascular disease and in the sympathectomized group, blood flow actually diminished after body heating, yet, in the majority of cases, Priscoline appeared to have an additive effect upon that produced by heating.

Summary and Conclusions

The effect of a vasodilating agent, Priscoline, was studied on four groups of subjects: normal individuals; patients with peripheral vasospastic disease; patients with organic disease of the peripheral arteries and patients before and after sympathectomy.

Values for peripheral blood flow and digital pulse volume were determined by means of a plethysmokymograph, utilizing the venous occlusion technic before and after vasodilatation produced by body heating and intramuscular Priscoline.

From the resulting data, the following conclusions may be drawn:

1. Priscoline produced significant increases in blood flow and pulse volume in normal subjects and certain patients.

2. Owing to the considerable variations in resting blood flow exhibited by normal subjects and patients, opinions regarding an agent or a procedure based on its effects on resting flow alone, should be guarded.

3. The use of indirect body heating is a practical and safe method for producing vasodilatation in the skin of the extremities. The "maximal flow" brought about by indirect heating is thought to be a reproducible standard of

reference against which the effect of Priscoline and other agents can be measured. The limitations of indirect heating as an effective vasodilating agent do not detract appreciably from its clinical usefulness.

4. The use of Priscoline in conjunction with the plethysmokymograph is found to be a convenient hospital procedure for the preliminary appraisal of peripheral circulatory status. At the same time it is helpful in predicting the probable therapeutic value of the drug for a given patient.

5. Digital plethysmography is a valuable adjunct to the study of peripheral arterial disease and the effects of various agents upon peripheral circulation.

REFERENCES

[1] GOETZ, R. H.: The diagnosis and treatment of vascular diseases with special consideration of clinical plethysmography and the surgical physiology of the autonomic nervous system. Brit. J. Surg. **37:** 25, 1949.

[2] LANDIS, E. M., AND GIBBON, J. H.: A simple method of producing vasodilatation in the lower extremities. Arch. Int. Med. **52:** 785, 1933.

[3] MEIER, R., AND MULLER, R.: Vascular effects of a new imidazoline derivative. Schweiz. med. Wchnschr. **69:** 1271, 1939.

[4] AHLQUIST, R. P., HUGGINS, R. A., AND WOODBURY, R. A.: The pharmacology of benzylimidazoline (Priscol). J. Pharmacol. & Exper. Therap. **89:** 271, 1947.

[5] NICKERSON, M.: The pharmacology of adrenergic blockade. J. Pharmacol. & Exper. Therap. **95:** 27, 1949.

[6] MURPHY, R. A., JR., MCCLURE, J. N., JR., COOPER, F. W., JR., AND CROWLEY, L. G.: Effect of priscoline, papaverine, and nicotinic acid on blood flow in lower extremity of man; comparative study. Surgery **27:** 655, 1950.

[7] GOETZ, R. H.: Plethysmography of the skin in the investigation of peripheral vascular diseases. Brit. J. Surg. **27:** 506, 1940.

[8] —: The rate and control of the blood flow through the skin of the lower extremities. Am. Heart J. **31:** 146, 1946.

[9] —: The rate and control of the blood flow through the skin of the upper extremities. South African J. M. Sc. **8:** 65, 1943.

[10] —, AND AMES, F.: Reflex vasodilatation by body heating in diagnosis of peripheral vascular disorders. Arch. Int. Med. **84:** 396, 1949.

Simplified Determination of Arterial Insufficiency

Plethysmographic Observation of Reactive Hyperemia following Fifteen Minute Arterial Occlusion at the Ankle

By TRAVIS WINSOR, M.D.

Reactive hyperemia following 15 minute arterial occlusion at the ankle was studied in plethysmographic tracings using the venous occlusion technic. The resulting curves present an essentially different pattern in normal subjects and patients with various types of peripheral arterial disease. Several characteristic features can be distinguished, notably the level of highest blood flow after release of arterial occlusion, the time required until the highest blood flow is reached, and the degree of secondary vasoconstriction. Evaluation of these factors permits an estimate of the therapeutic value of lumbar sympathectomy.

PLETHYSMOGRAPHIC observation of transient reactive hyperemia elicited through arterial occlusion has for many years been employed to determine the degree of vascular response and to estimate the therapeutic effect which may be expected from various medical and surgical procedures. The method was greatly improved by the development of the technic of venous occlusion.[1] Other technics proposed include injection of vasodilating drugs,[2] lumbar sympathetic block, posterior nerve block, spinal,[3] sacral, or paravertebral anesthesia.

Many of these procedures require the personal supervision of a physician, and in some cases the element of hazard cannot be entirely excluded. With the introduction of the pneumoplethysmograph[4] it has become possible to devise a standardized, simple and safe method for the determination of arterial insufficiency, which can be entrusted to a well-trained technician without requiring the immediate attention of a physician. Five minute arterial occlusion with the cuff applied above the knee is essentially satisfactory,[3] but produces submaximal vasodilatation, and the vascular response is in some cases appreciably influenced by pain at the site of the occluding cuff. It was therefore decided to test a modified technic employing arterial occlusion for a period of 15 minutes with the cuff at the ankle, a site at which pain is much less frequently observed.

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METHOD AND MATERIALS

In a comfortable environment[6] with a mean room temperature of 26 C. ± 1.5 C., determinations were carried out on 156 individuals (table 1) who had been made to rest for a period of 45 minutes, covered with wool blankets. The arterial cuff at the ankle was inflated to 100 mm. Hg above the arterial systolic pressure as ascertained by the plethysmographic technic.[7] Occlusion was maintained for 15 minutes and the string shadow frequently checked for any sign of drift indicating arterial leakage. The skin temperature was measured simultaneously with an electronic recorder. A fall of 2 C. was ordinarily observed in individuals with a resting skin temperature distinctly above room temperature, and was taken to mean that no gross leaks of arterial blood had occurred.

Following release of arterial occlusion the relative blood flow was measured by applying a venous collecting cuff at the ankle. The cuff was rapidly inflated for two to three seconds to a pressure of 60 mm. Hg in subjects without arterial disease,

while in patients with arterial disease lower pressures were employed (not less than 35 mm. Hg) for longer periods of time. Volume changes of the digit were recorded at intervals of from 15 seconds to 1 minute for a period of 10 minutes. The rate of filling of the digit was calculated from the slant of the base line in cu. mm. per 5 cc. of tissue per second. Prior to the test, the volume of the toe was carefully measured and the instrument accurately standardized.

TABLE 1.—*Number and Ages of Subjects Studied Employing 15 Minute Arterial Occlusion at the Ankle for Production of Reactive Hyperemia.*

	Number of Determinations	Age of Subjects
Normal Individuals	26	18–54 Average: 30
Arteriosclerosis Obliterans	100	20–65 Average: 45
Vasoneurosis	5	18–30 Average: 22
Raynaud's Phenomenon due to Thromboangiitis Obliterans	5	27–51 Average: 36
Arteriosclerosis Obliterans Treated by Lumbar Sympathectomy	20	30–60 Average: 39
Total	156	

RESULTS

Maximum Rate of Toe Flow

The changes in the blood flow to the toe before and after arterial occlusion (fig. 1*B*) in a normal individual are correlated with the changes in amplitude of the pulse wave and in the total volume of the digit (fig. 1*A*). It should be mentioned that diastolic periods appear in the plethysmographic curves, in which the pulse recorder is running horizontally, denoting absence of blood flow; but this well known "standard error" may be neglected for the purpose of clinical evaluation. After release of occlusion the volume of the digit increased rapidly, while the amplitude of pulse waves reached a maximum about two minutes later. Blood flow to the toe arrived at a peak of 32 cu. mm. per second after forty-five seconds; it decreased gradually to 7 cu. mm. per second, rising again to 9 cu. mm. per second after four minutes. This phase of decline of the flow rate below the resting level is probably due to vasoconstriction—an assumption confirmed by the finding that in a representative group of patients with arteriosclerosis obliterans treated by lumbar sympathectomy, blood flow to the toe never declined during reactive hyperemia below the resting level (fig. 2). Throughout the four minute period following release of occlusion, respiration, alpha and beta waves appeared in the plethysmogram of normal patients, suggesting vasomotor activity due to sympathetic activity.

Fifteen-minute arterial occlusion was performed five days in succession and under uniform conditions in healthy individuals and patients with arteriosclerosis obliterans without ulceration of the toes. The daily variations in each case were comparatively small, thus demonstrating the reproducibility of the technic.

The characteristic features of reactive hyperemia in *normal subjects*, following 15 minute arterial occlusion at the ankle are presented in a group of 5 typical cases, with ages ranging from 18 to 34 years (fig. 3). The mean resting blood flow was 7.8 cu. mm. per 5 cc. per second, the maximum toe flow amounted on the average to 20.8 cu. mm. (19.0 to 24.2 cu. mm.), and was reached after 0.68 minute (0.38 to 1.0 minute). During the vasoconstrictive phase the toe flow declined on the average to 4.1 cu. mm. (2.0 to 6.0 cu. mm.).

These values represent normal blood flow through normally patent vessels under normal nervous vascular control. Curves of unusual configuration can be produced by deep breathing or breath holding, a startling sound, a disturbing light, or application of cold, or painful heat to the body during the phase of reactive hyperemia. Higher readings are generally obtained a few hours after a heavy protein meal; unusually low values result when the test is performed without preceding rest, during pain, anxiety, or soon after smoking.

During the period of occlusion the toe presented a cyanotic appearance, but erythema developed rapidly with reactive hyperemia and a palpable increase in temperature was noted. Continuous recordings showed that the skin temperature returned to the resting level six minutes after release of occlusion and then proceeded to rise gradually to a highest value,

approximately 2 C. above the control temperature.

Reactive hyperemia in patients with *arteriosclerosis obliterans without demonstrable tissue changes of the toes* is presented in a group of 4 typical cases (fig. 4). In these patients blood flow to the toe rises slowly to a comparatively low maximum rate, and the vasoconstrictive phase is somewhat less pronounced than in normal individuals.

Fifteen minute arterial occlusion at the ankle was also produced in 50 other patients with arteriosclerosis obliterans. In many cases blood flow to the toe following release of the arterial cuff became apparent only after an interval of seconds or even minutes. This condition, called "anemocyclia"[6] is encountered in patients with advanced arterial disease and is associated with an unusually small rate of arterial inflow as well as with a low maximum rate of toe flow. Anemocyclia, however, is also observed in the plethysmogram of subjects without organic arterial disease, but suffering from pronounced vasospasm of the toes. In the latter group the plethysmographic curve returns to almost normal following intense body heating (fig. 5*E*), while in arteriosclerosis obliterans the degree of anemocyclia is only slightly modified.

Clinically the appearance of erythema following release of the cuff was delayed. Measurements of the skin temperature taken in all

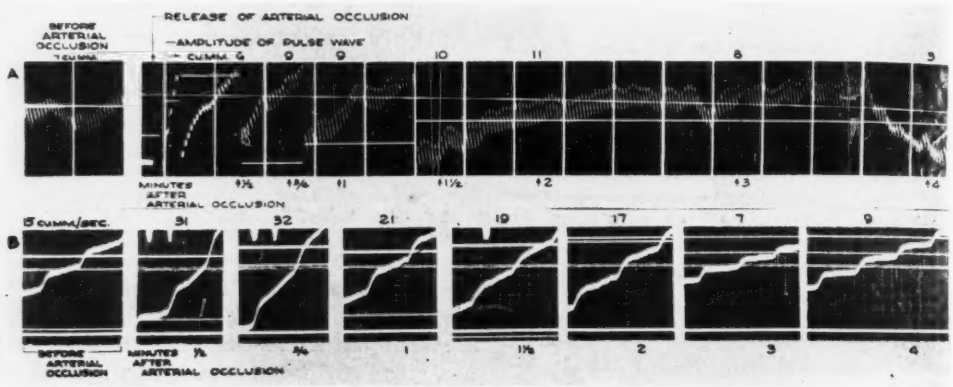

FIG. 1. Reactive hyperemia in a normal individual, following 15 minute arterial occlusion at the ankle. *A*. Changes in the amplitude of the pulse wave and in the total volume of the digit, before and after arterial occlusion. *B*. Changes in the blood flow to the toe, before and after arterial occlusion.

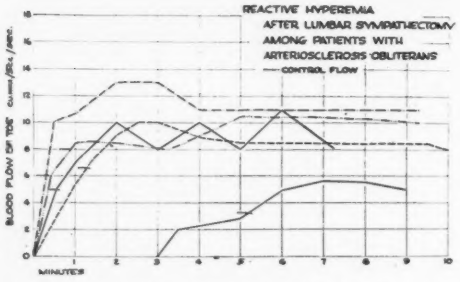

FIG. 2. Reactive hyperemia following 15 minute arterial occlusion at the ankle, in a group of 15 patients with arteriosclerosis obliterans, three months to three years subsequent to lumbar sympathectomy.

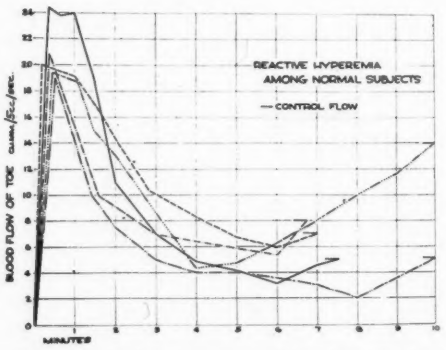

FIG. 3. Reactive hyperemia following 15 minute arterial occlusion at the ankle, in a group of 5 normal subjects.

51 patients showed that the rate of cooling of the digit during arterial occlusion did not differ significantly from that observed in normal individuals. On the average, however, the skin temperature rose in this group after release of the cuff 0.2 C. above the control level as compared to 2.1 C. in normal subjects with similar control temperatures (32 to 33 C.). Due to the subnormal rate of blood flow[9] the control level was reached in patients with peripheral arterial disease in 12.8 minutes, as against 6.2 minutes in normal subjects.

Following lumbar sympathectomy patients with arteriosclerosis obliterans present a fairly elevated resting blood flow. After 15 minute arterial occlusion at the ankle blood flow to the toe rises slowly to a comparatively high maximum rate, while secondary vasoconstriction is entirely absent (fig. 2).

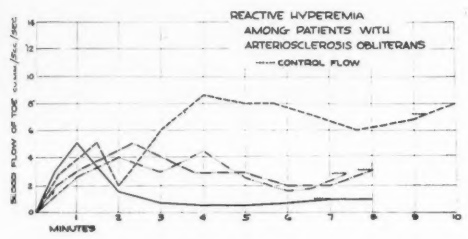

FIG. 4. Reactive hyperemia following 15 minute arterial occlusion at the ankle, in a group of 4 patients with arteriosclerosis obliterans without demonstrable tissue changes of the toes.

The maximum rate of blood flow reached during reactive hyperemia represents the net effect of the interaction between vasodilating influences, probably due to the release of a humoral substance of histamine-like character, and vasoconstricting influences traceable to sympathetic nervous activity. In normal subjects the rate of blood flow to the toe rises immediately, culminates quickly, and secondary vasoconstriction occurs four to six minutes after release of arterial occlusion. The characteristic pattern in patients with arteriosclerosis obliterans shows slow filling of the vascular bed and a low maximum rate of blood flow; in individual cases the configuration of the plethysmographic curve depends mainly on two factors: the caliber of the large arteries supplying the digit, and the degree of vasodilatation produced by release of arterial occlusion.[10] The curve is furthermore modified by the degree of tissue distensibility as well as the amount of hyperemia existing as a result of disease prior to 15 minute arterial occlusion.

The highest rate of blood flow to the toe during reactive hyperemia differs considerably in patients with arteriosclerosis obliterans *without* and *with* tissue changes of the toes. In the first group the highest rate amounted on the average to 12.2 cu. mm. per 5 cc. per second (limits: 5.0 to 17.0), while in the latter group the average was 1.9 cu. mm. per 5 cc. per second (limits: 0.1 to 6.0). Any relation

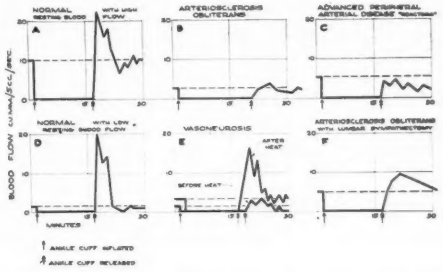

FIG. 5. Blood flow debt and repayment following 15 minute arterial occlusion at the ankle in normal individuals with high resting blood flow (*A*); normal individuals with low resting blood flow (*D*); patients with arteriosclerosis obliterans (*B*); patients with vasoneurosis (*E*); patients with advanced peripheral arterial disease: "reactors" (*C*); and patients with arteriosclerosis obliterans treated by lumbar sympathectomy (*F*).

between clinical appearance and degree of reactive hyperemia, however, must be cautiously evaluated. The state of the tissues does not depend exclusively upon the maximum rate of blood flow possible following release of arterial occlusion; many other factors have to be considered, especially the amount of exercise which the patient has taken, previous application of heat, prolonged foot soaks, infection, trauma, the presence or absence of metabolic changes and the duration of vasoconstriction.

Among patients with arteriosclerosis obliterans *without* tissue changes the rate of highest blood flow varied considerably. Tissue changes were sometimes absent even though a flow as low as 5.0 cu. mm. per 5 cc. per second was

observed following release of arterial occlusion. The peak flow was never reached in less than one minute, and sometimes only after an interval of four minutes.

Tissue changes accompanying arteriosclerosis obliterans consisted mostly of erythema with diapedesis of red cells into the subcutaneous layers which did not blanch on pressure. If this was the result of arterial insufficiency and not of external causes, the highest blood flow was always lower than 6 cu. mm. per 5 cc. per second and was reached in a very slow rise. Occasionally, transition from normal clinical appearance of the toes to demonstrable changes in the tissues of the digit is observed without variation in the level of the highest flow rate.

Blood Flow Debt and Repayment

Hyperemia following arterial occlusion at the ankle was also studied in order to ascertain whether the net effect of the technic amounted to an increase or a decrease of blood flow to the digit. Bier reported that the net effect of this entire procedure is an increase in the blood flow, and built a therapeutic procedure upon that premise.[11]

If, indeed, an actual increase in blood flow would take place, the rise above the control level in the period of reactive hyperemia (repayment) would have to be in excess of the amount of blood withheld during arterial occlusion (blood flow debt). A rough estimate of this ratio is possible through graphic representation of the plethysmographic values obtained.

Among 5 normal individuals with high resting blood flow, age 23 to 33 years (fig. 5*A*), the debt exceeded the repayment. The deficit would be still more accentuated and the repayment even less significant if, in estimating the blood flow debt, one were also to take into consideration the phase of secondary vasoconstriction. Among 5 normal subjects with low resting blood flow, age 31 to 35 (fig. 5*D*), the debt was small and the repayment large, owing to the low control level. Among 10 patients with arteriosclerosis obliterans, age 35 to 60 (fig. 5*B*), the blood flow debt was often increased due to anemocyclia. Repayment was consistently small, probably because the effect of acute ischemia induced through arterial occlusion must remain marginal in the presence of chronic ischemia due to pathologic processes. Among 5 individuals, age 18 to 30 years (fig. 5*E*) with intense vasoneurosis (originating from a pathologic state of anxiety) whose hands and feet were characteristically cold and clammy, the reactive hyperemia curve was often identical with that of patients with organic peripheral disease. However, after prolonged rest and application of heat to the body the curve in the former group was transformed into one resembling the normal. Blood flow debt and repayment in this group of patients vary considerably, depending on the level of the resting blood flow, the degree of spasm, and the conditions under which the test is performed. Another group of cases presents unusually pronounced vasoconstriction after release of the arterial cuff; it is mainly composed of patients with Raynaud's phenomenon due to thromboangiitis obliterans, but probably also includes subjects with advanced arterial disease of any type. Among 5 "reactors," ages 27 to 51 years (fig. 5*C*), blood flow following release of arterial occlusion did not reach the control level during the test period, which in other groups is characterized by reactive hyperemia of varying degrees; thus no repayment occurred and the blood flow debt was still increased after release of occlusion. Patients of this type are often hypersensitive to emotional disturbances or touch, and vasoconstriction may well represent an abnormal response to pressure applied at the ankle. In this group, vasospasm was much less pronounced following lumbar sympathetic block or posterior tibial nerve block using Novocain, a finding suggesting that vasoconstriction is at least partly of nervous origin. Vasospasm was, on the other hand, accentuated when the occluding cuff was placed at the base of the toe instead of the ankle; this is probably due to direct pressure on the smaller vessels close to the recording cup. Among 20 patients, ages 30 to 60 years (fig. 5*F*), with arteriosclerosis obliterans treated by lumbar sympathectomy, the control level was high and repayment proportionately small.

The different theories brought forward in an attempt to account for the variations in blood

flow debt and repayment have been discussed at length by Abramson.[1] It seems probable that in the presence of a blood flow debt there occurs also a metabolic debt, but in none of the 156 cases in this series were clinically demonstrable ill effects from this procedure observed.

Discussion and Summary

The technic of 15 minute arterial occlusion at the ankle combined with intermittent venous occlusion following release of the arterial cuff has proved to be a simple, rapid, and reliably reproducible laboratory procedure. It can be carried out by a well trained technician without supervision of the physician. Reactive hyperemia produced by this technic results in plethysmographic data which are characteristically different for normal individuals, patients with arteriosclerosis obliterans, subjects with vasoneurosis, and patients with arteriosclerosis obliterans treated by lumbar sympathectomy. The curves of patients with arteriosclerosis obliterans and of subjects with vasoneurosis without arterial disease are under ordinary circumstances very similar, but can be differentiated through application of heat to the body prior to repeated performance of the test.

Reactive hyperemia following 15 minute arterial occlusion at the ankle leads essentially to identical results when the test is reproduced on successive days under standard conditions in normal individuals or patients with peripheral arterial disease. If, on the other hand, tests are performed in patients at regular intervals, the change in the hyperemia curve will furnish an indication as to progression or regression of the disease. For instance, in the case of a 48 year old man with popliteal embolism due to posterior myocardial infarct of three months' duration, no reactive hyperemia was recorded. Subsequent to lumbar sympathectomy there occurred first a two minute period of anemocyclia, followed by a rise of blood flow to a highest rate of 8 cu. mm. per 5 cc. per second, reached after three minutes. One year later anemocyclia was reduced to one minute and a maximum flow of 10 cu. mm. per 5 cc. per second was attained after 2.2 more minutes. The patient lived with a useful limb until he succumbed to a myocardial infarct two years postoperatively.

The configuration of the reactive hyperemia curves thus indicates the state of peripheral circulation and makes it possible to choose between the various therapeutic agents and procedures available. This applies in particular to an estimate of the probable outcome of sympathetic surgery.[12] The method, furthermore, proves of value in establishing the degree of dilatation which may be elicited in patients previously treated by sympathectomy.

When anemocyclia fails to disappear following body heating or medication with ganglionic blocking agents, the disease process is far advanced and only relatively poor results can be expected from sympathectomy. The same applies to cases with a highest flow rate below 4 or 5 cu. mm. per 5 cc. per second. Surgical intervention, however, is often advisable if such a low maximal flow rate represents an increase of the resting blood flow to four or five times its previous value. Absence of secondary vasoconstriction, particularly in patients in whom it coincides with a low maximal flow rate, is often followed by poor operative results. In cases of this kind the endings of the sympathetic nerves have been destroyed, as for instance in certain types of peripheral vascular disease secondary to diabetes, or in the presence of pronounced rigidity of the vessel walls. Lumbar sympathectomy, on the other hand, ordinarily leads to satisfactory results in patients without true anemocyclia and with a maximal blood flow of from 6 to 17 cu. mm. per 5 cc. per second. Pronounced vasodilatation is observed in the first few postoperative days, declining during the next few weeks; but the rate of blood flow with the patient at rest remains in almost all instances for months or years considerably higher than prior to surgery.

A comparison of the highest skin temperatures reached after release of 15 minute arterial occlusion at the ankle with the maximum reading after posterior tibial nerve block using Novocain shows that the latter technic results in considerably higher skin temperatures while the blood flow is slightly lower. This

finding suggests that arterial occlusion produces a relatively greater flow through the deeper tissues of the toe than through the superficial layers of the skin. The difference may, on the other hand, be due to the fact that the plethysmographic technic is more sensitive in recording rapid changes in blood flow than measurements of the skin temperature, as some time is required until changes in the rate of blood flow manifest themselves in an increased temperature of the tissues of the toes.

A study of blood flow debt and repayment during reactive hyperemia demonstrated that this method is not indicated in the treatment of patients with organic arterial disease. No deleterious effects were noted, on the other hand, following arterial occlusion for a period of 15 minutes, even in patients with far advanced arterial disease. This diagnostic technic may therefore be regarded as safe and effective.

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REFERENCES

[1] ABRAMSON, D. I.: Vascular Responses in the Extremities of Man in Health and Disease. Chicago, University of Chicago Press, 1944.

[2] WINSOR, T.: Newer methods for selection of patients for lumbar sympathectomy. California Med. **72:** 342, 1950.

[3] SOLOFF, L. A., BURNETT, W. E., AND BELLO, C. T.: Study of the comparative value of tetraethylammonium bromide and diagnostic spinal anesthesia in the selection of hypertensive persons for sympathectomy. Am. J. M. Sc. **216:** 665, 1948.

[4] BURCH, G. E.: New sensitive portable plethysmograph. Am. Heart J. **33:** 48, 1947.

[5] KONDO, B., WINSOR, T., YAMAUCHI, P., MORRISON, R. E., AND RAULSTON, B. O.: Five-minute arterial occlusion technique for the determination of vascular insufficiency. Am. Heart J. **39**: 99, 1950.

[6] NEUMANN, C., COHN, A. E., AND BURCH, G. E.: Study of influence of character of examining room on peripheral blood vessels of normal, hypertensive, and senile subjects. J. Clin. Investigation. **21:** 651, 1942.

[7] WINSOR, T.: Influence of arterial disease on the systolic blood pressure gradients of the extremity. Am. J. M. Sc. **220:** 117, 1950.

[8] ——, MORRISON, R. E., KONDO, B., AND YAMAUCHI, P.: Arterial insufficiency studied by several plethysmographic techniques employing occlusion of the arteries of the extremity. Am. J. M. Sc. **219:** 473, 1950.

[9] EVANS, W. F., AND STEWART, H. J.: Peripheral blood flow in case of adrenal pheochromocytoma before and after operation. Am. Heart J. **24:** 835, 1942.

[10] LANDOWNE, M., AND KATZ, L. N.: Critique of plethysmographic method of measuring blood flow in extremities of man. Am. Heart J. **23:** 644, 1942.

[11] MEYER, W., AND SCHMIEDEN, V.: Bier's Hyperemic Treatment. Philadelphia, W. B. Saunders, 1908.

[12] FINDLEY, T.: Sympathectomy and the ischemic extremity. Nebraska State M. J. **34:** 379, 1949.

Ammonium Chloride Acidosis

A Report of Six Cases

By MARVIN H. SLEISENGER, M.D., AND A. STONE FREEDBERG, M.D.

The administration of 6 to 8 Gm. of enteric coated ammonium chloride daily for 7 to 45 days to 6 patients resulted in severe, and in 2 instances nearly fatal, acidosis. Five of the 6 patients had congestive heart failure and one, subacute glomerulonephritis; each of the 5 patients with congestive failure had organic renal disease. The clinical manifestations, differentiation from the low salt syndrome and the therapy are discussed.

SINCE the demonstration of the diuretic effect of certain acid producing salts, ammonium chloride has been used extensively in the treatment of edema, particularly in congestive heart failure.[1] Its use in this condition is principally in association with mercurial diuretics; it enhances the effect of these drugs by maintaining a normal or replenishing a depleted blood chloride concentration.[2, 3]

In 1925, Keith and his co-workers[4] reported the occurrence of severe acidosis and azotemia in a patient suffering from nephritis and edema treated with 25 Gm. of ammonium chloride over a five day period; the blood carbon dioxide combining power fell to 9 volumes per cent and the blood nonprotein nitrogen rose to 276 mg. per hundred cc. Various recent textbooks[5-8] point out the danger of inducing acidosis by ammonium chloride administration in patients with renal disease.

During the past 15 months, 6 patients have been observed at the Beth Israel Hospital with severe and, in 2 cases, nearly fatal acidosis following the administration of 6 to 8 Gm. of ammonium chloride daily for periods of 7 to 45 days. Five of the 6 patients had congestive heart failure and various types of intrinsic renal disease; the remaining patient, case 4, had subacute glomerulonephritis and anasarca.

During the period of these observations, ammonium chloride has been administered in tablets whose enteric coating is stated to be more uniformly soluble; in consequence more regular and rapid absorption has been achieved.[9] Furthermore, the clinical impression has been gained that the lack of absorption evident in the past by the finding by x-ray of tablets in the colon and the passing of undissolved tablets in the feces has been overcome by these changes in the coating. The appearance of significant acidosis in patients treated with ammonium chloride warrants, in view of its widespread use, a report of the observations in these patients.

From the Medical Research Department, Yamins Research Laboratory, Beth Israel Hospital, and the Department of Medicine, Harvard Medical School, Boston, Mass.

CASE REPORTS

Case 1. P. W., BIH #M8286, an 85 year old man, entered the hospital on Oct. 1, 1949 because of acute urinary retention of 36 hours' duration. He had had mild congestive heart failure and angina pectoris observed in the cardiac clinic for the previous five years.

On physical examination, the heart was enlarged to the left, the rhythm regular and there was a harsh apical systolic murmur transmitted over the precordium. The blood pressure was 140/60. The lungs were clear. A tender liver edge was felt 4 fingerbreadths below the right costal margin. There was 2 plus pitting edema over the sacrum. The urinary bladder was distended. The prostate was normal in size, shape and consistency.

Laboratory Studies. The urine specific gravity varied from 1.002 to 1.010. There was 2 to 4 plus albuminuria. The sediment contained few to many white and red blood cells. Repeated urine cultures were positive for *Bacillus coli*, *Proteus vulgaris*, or *Pseudomonas aeruginosa*. The blood nonprotein nitrogen was 45 mg. per hundred cc. A chest roentgenogram showed enlargement of the heart to the left; there was no pulmonary congestion. An electrocardiogram was consistent with left ventricular hypertrophy.

Clinical Course. The patient was catheterized (1200 cc. urine obtained) and placed on constant urinary bladder drainage, a maintenance dose of digitalis daily, ammonium chloride and a low salt

diet. The daily urinary output during the first four hospital days varied from 1000 to 1400 cc. Forty-two Gm. of ammonium chloride were administered from the fourth to the eleventh hospital days. On the sixth hospital day, after two days of ammonium chloride, the urinary output fell to 500 cc. From the sixth to the eleventh hospital day, although the urinary output increased with increased fluid administration to 2500 cc., the patient became increasingly somnolent and apathetic. On the eleventh hospital day the patient was alternately confused,

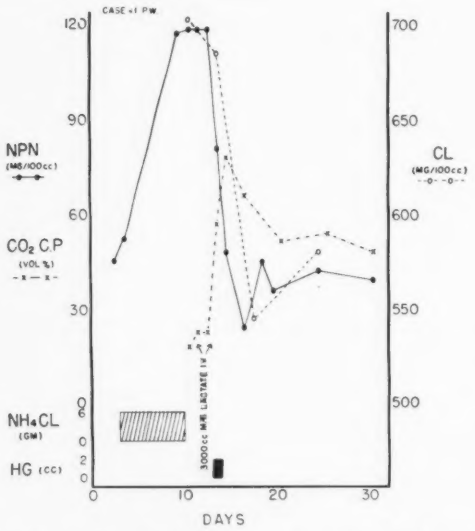

FIG. 1. The clinical course, ammonium chloride administration, and laboratory findings in P.W., case 1. Following the cessation of ammonium chloride therapy and after the administration of one-sixth molar lactate solution intravenously, there is a prompt rise in carbon dioxide combining power and a fall in the nonprotein nitrogen to normal values. One injection of 2 cc. Mercuhydrin intramuscularly (Hg. cc.) was given on the fourteenth hospital day, four days after ammonium chloride was omitted.

disoriented and deeply stuporous but could be aroused. Cheyne-Stokes respiration was present. The lungs were clear and there was no peripheral edema. At this time, the nonprotein nitrogen was 124 mg. per hundred cc. and the blood carbon dioxide combining power was 19 volumes per cent (fig. 1). The blood chloride was 708 mg. per hundred cc. Ammonium chloride was discontinued and during the subsequent 24 hours the patient received 24 Gm. sodium bicarbonate orally. During each of the subsequent two days, two and three days after omission of ammonium chloride, 3000 cc. one-sixth molar lactate solution was administered intravenously. Within 48 hours of this therapy, there was complete clinical recovery from acidosis (fig. 1). There was no recurrence of peripheral edema. Transurethral prostatic resection was successfully accomplished on the twenty-eighth hospital day and the patient was discharged to the Outpatient Medical Department.

Case 2. R. B., BIH #M6711, a 68 year old woman with mild diabetes mellitus and hypertension of many years' duration, albuminuria of at least one year's duration, angina pectoris for the previous two years, and recurrent acute pulmonary edema for one year, entered the hospital on June 20, 1949 because of crushing, severe, substernal pain, weakness, pallor, sweating, dyspnea and acute pulmonary edema.

On physical examination the patient was dyspneic, orthopneic and cyanotic. The heart was enlarged to the left, the rhythm regular; there was a grade II apical systolic murmur. There were moist rales at both lung bases. The liver edge was 3 fingerbreadths below the right costal margin. There was no peripheral edema.

Laboratory Studies. Three urine examinations showed 3 to 4 plus albumin, normal specific gravity, and negative sediments. The blood nonprotein nitrogen was 54 mg. per hundred cc. Repeated electrocardiograms showed S-T segment and T wave changes consistent with the clinical diagnosis of recent myocardial infarction. A chest roentgenogram showed cardiac enlargement to the right and left and an increase in the hilar shadows consistent with pulmonary congestion.

Clinical Course. The patient was treated with 0.1 Gm. digitalis leaf daily, ammonium chloride 6 Gm. daily, a low salt diet and intermittent injections of Mercuhydrin intramuscularly. The pulmonary edema present on entry cleared rapidly. Insulin was not required at any time during the hospital stay; repeated urine examinations were negative for acetone and sugar (a rare specimen gave a green reduction of Benedict's reagent). Sixty-four Gm. of ammonium chloride were given from the second through the eleventh hospital days. On the tenth day, after 54 Gm. ammonium chloride had been administered, the patient became confused, somnolent and, during the next several days, stuporous. On the twelfth hospital day, the patient was semicomatose, unresponsive and areflexic; the respirations were Kussmaul in type. The blood nonprotein nitrogen was 54 mg. per hundred cc., the blood carbon dioxide combining power was 16 volumes per cent, and the blood chloride was 680 mg. per hundred cc. Ammonium chloride was discontinued. The intravenous administration of 3000 cc. one-sixth molar lactate solution during the subsequent 48 hours was associated with rapid clinical recovery. The patient became responsive and alert and the respirations and reflexes returned to normal. The carbon dioxide combining power 96 hours after

cessation of ammonium chloride and 48 hours after intravenous lactate solution was 54 volumes per cent. The patient was discharged, improved, on the twenty-sixth hospital day.

Case 3. B. D., BIH #M7251, a 67 year old woman, re-entered the hospital on July 2, 1949 because of progressive ascites, ankle edema and orthopnea of five and one-half months' duration. One year before, 15 mc. I^{131} had been administered for hyperthyroidism. Ten months before, she had entered the hospital with acute hepatitis and jaundice.

On physical examination the blood pressure was 140/82. The heart was enlarged to the anterior axillary line; there was a grade III blowing apical systolic murmur. The rhythm was regular. There were moist rales at both lung bases. The liver edge was palpable 4 fingerbreadths below the right costal margin; the spleen was felt 1½ fingerbreadths below the left costal margin. There was moderate ascites but no peripheral edema.

Laboratory Examinations. Six specimens of urine had a specific gravity of 1.010 or less with 1 to 2 plus albumin in all specimens. Blood nonprotein nitrogen was 62 mg. per hundred cc. and blood chloride 576 mg. per hundred cc. The hemoglobin was 7.1 Gm. per hundred cc. (Evelyn); the red blood cell count was 2 million per cu. mm. A chest roentgenogram showed marked dilation of the heart to the left and right with increased lung markings consistent with pulmonary congestion. An electrocardiogram was within normal limits.

Clinical Course. The patient was treated with a high calorie, low salt diet, digitoxin and intermittent injections of Mercuhydrin intramuscularly with a consequent marked diuresis. Thirty-four Gm. of ammonium chloride were administered from the ninth to the fourteenth hospital days. On the eleventh hospital day the nonprotein nitrogen was 85 mg. per hundred cc. and on the thirteenth hospital day was 107 mg. per hundred cc. On the fourteenth hospital day anorexia, nausea and lassitude were present and the ammonium chloride was discontinued. The following day, the fifteenth hospital day, the carbon dioxide combining power was 26 volumes per cent. Following the intravenous administration of 3000 cc. 5 per cent glucose and 500 resuspended red blood cells, prompt disappearance of the anorexia, nausea and lassitude occurred. The carbon dioxide combining power 24 hours after cessation of ammonium chloride therapy and after fluid administration rose to 43 volumes per cent. The blood nonprotein nitrogen fell slowly over a period of 10 days to 54 mg. per hundred cc. The patient was discharged on the twenty-fifth hospital day to the Nephritic Clinic.

Case 4. E. K.,* BIH #M5045, a 25 year old man, entered the hospital on March 18, 1949 because of massive edema of three months' duration. Four and one-half months prior to entry he had had acute glomerulonephritis. On entry there was generalized anasarca, ascites, and edema of the face and eyelids. Blood pressure was 164/112.

Laboratory Studies. Forty-six speciments of urine showed persistent 4 plus albuminuria and finely granular and hyaline casts; occasional urine sediments contained up to 10 red blood cells per high power field. Blood nonprotein nitrogen was 43 mg. per hundred cc. and the blood chloride was 680 mg. per hundred cc. Serum cholesterol was 374 mg. per hundred cc. A chest roentgenogram showed the heart to be normal in size and shape.

Clinical Course. The patient was treated with ammonium chloride, 6 Gm. daily, and frequent mercurial injections (Hg in fig. 2) with a marked

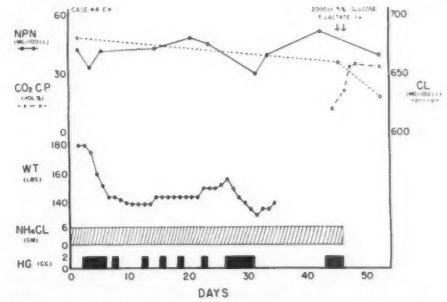

FIG. 2. The acidosis consequent to ammonium chloride administration in E. K., case 4. Two Gm. of ammonium chloride administered on the morning of the forty-seventh hospital day are not illustrated in the figure. Note the prompt rise in carbon dioxide combining power following omission of ammonium chloride and after the administration of fluids and lactate solution intravenously.

diuresis and weight loss (fig. 2). The blood pressure fell to normal. Two-hundred seventy-eight Gm. of ammonium chloride were administered from the first through the forty-seventh hospital day. On the forty-seventh hospital day, the patient was nauseated, anorexic and stuporous. Kussmaul respiration was present. The daily urinary output during the preceding week varied from 1100 to 3700 cc. The carbon dioxide combining power was 13 volumes per cent and the blood chloride was 658 mg. per hundred cc. Rapid clinical improvement and relief of the symptoms and laboratory evidence of acidosis (fig. 2) followed the discontinuance of ammonium chloride and the intravenous administration of 4000 cc. 5 per cent glucose and 320 cc. molar lactate in the next 48 hours. The urinary output during the preceding two days and subsequent week averaged 2000 cc. daily. The subsequent clinical course was complicated by the develop-

* Referred by Dr. Harry Derow.

ment of multiple abscesses and peripheral thrombophlebitis. He was discharged on the one hundred thirteenth hospital day. Although improved, ascites was still present and 1 plus to 2 plus peripheral edema was present.

Case 5. H. S., BIH #M3398, a 55 year old man with rheumatic heart disease, marked cardiac enlargement, mitral stenosis and insufficiency, aortic stenosis and insufficiency, chronic congestive heart failure, and old right popliteal artery embolism, re-entered the hospital on April 2, 1949 because of recurrent congestive heart failure.

On physical examination he was orthopneic and slightly cyanotic. Cardiac murmurs of mitral and aortic stenosis and insufficiency were present. The liver was palpable 3 fingerbreadths below the right

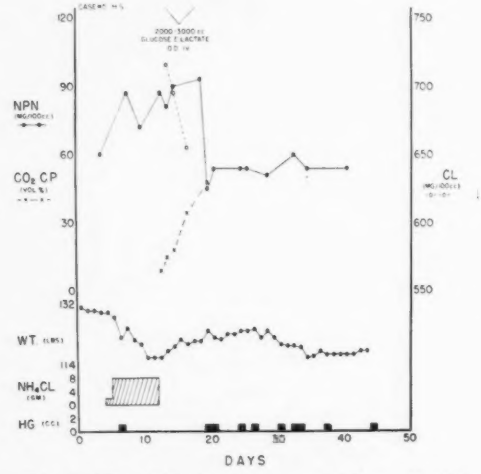

FIG. 3. The clinical course, ammonium chloride administration, and laboratory findings in H. S., case 5. (See text for description.)

costal margin; the spleen was felt 2 fingerbreadths below the left costal margin. There was a slight peripheral pitting edema. Blood pressure was 150/90.

Laboratory Data. Sixteen specimens of urine showed persistent 3 to 4 plus albumin, fixed low specific gravity (1.010 to 1.011) and granular and hyaline casts with a few red and white blood cells. Blood nonprotein nitrogen was 60 mg. per hundred cc. The hemoglobin was 7.0 Gm. per hundred cc. and the red blood cell count was 3.5 million per cu. mm.

Clinical Course. The patient was treated with digitoxin, oxygen, a low salt diet, ammonium chloride, 8 Gm. daily, and intermittent injections of Mercuhydrin (Hg in fig. 3) with a marked diuresis and weight loss (fig. 3). Fifty-eight Gm. of ammonium chloride were administered from the fifth through the twelfth hospital days. On the twelfth hospital day the patient was stuporous, nauseated, vomiting, and appeared critically ill. Kussmaul respiration was present. The urinary output during this day and the preceding two days was above 1100 cc. daily. The blood carbon dioxide combining power was less than 10 volumes per cent, the nonprotein nitrogen was 88 mg. per hundred cc. and the blood chloride was 716 mg. per hundred cc. Ammonium chloride therapy was discontinued and progressive clinical and laboratory recovery was associated with the administration of 5 per cent dextrose in water and one-twelfth molar lactate solution (2000 to 3000 cc. daily) intravenously during the period of a week (arrowhead, fig. 3). There was, however, gain in weight, persistent basal pulmonary rales and peripheral edema which responded slowly to frequent injections of Mercuhydrin (fig. 3).

The patient reentered the hospital four months later and expired in congestive heart failure and uremia. Autopsy revealed rheumatic heart disease, cardiac enlargment with mitral and aortic stenosis, passive congestion of the viscera and chronic glomerulonephritis.

Case 6. I. R.,* BIH #M1676, a 67 year old woman with diabetes mellitus for the previous 20 years, hypertension and albuminuria for two years, entered the hospital on Aug. 10, 1948 because of severe congestive heart failure, paroxysmal nocturnal dyspnea and general anasarca of four months' duration.

On physical examination the patient was orthopneic, dyspneic and slightly cyanotic. The heart was markedly enlarged. There was a right hydrothorax. A tender liver edge was felt 6 fingerbreadths below the right costal margin. There was marked peripheral pitting edema. Blood pressure was 120/90.

Laboratory Data. The urine showed 1 to 4 plus albumin with occasional clumps of white blood cells and granular casts. The specific gravity varied from 1.008 to 1.023. The blood nonprotein nitrogen was 40 mg. per hundred cc. A chest roentgenogram showed a right pleural effusion and cardiac enlargement to the left. The aortic arch was widened and calcified.

Clinical Course. The administration of whole leaf digitalis, a low salt diet, 8 Gm. of ammonium chloride daily and intermittent injections of Mercuhydrin (Hg in fig. 4) intramuscularly was associated with an excellent diuresis (fig. 4) and clinical improvement. Protamine zinc insulin (16 to 32 units) was administered daily, with adequate control of the diabetes. The urine examinations were consistently negative for acetone and a green reduction of Benedict's reagent was obtained occasionally. One hundred thirty-six Gm. of ammonium chloride were administered from the third through the nineteenth hospital day (fig. 4). On the seventeenth

* Referred by Dr. Joseph E. F. Riseman.

hospital day the patient was noted to be increasingly drowsy and anorexic. On the twentieth hospital day the blood carbon dioxide combining power was 5 volumes per cent, and the blood nonprotein nitrogen was 61 mg. per hundred cc. Ammonium chloride was discontinued. The intravenous administration during each of the subsequent three days of 3000 cc. 5 per cent glucose in water to which were added 3 to 6 ampoules of Ringer's lactate solution resulted in rapid relief of the drowsiness and anorexia. The blood carbon dioxide combining power and nonprotein nitrogen returned to normal values (fig. 4).

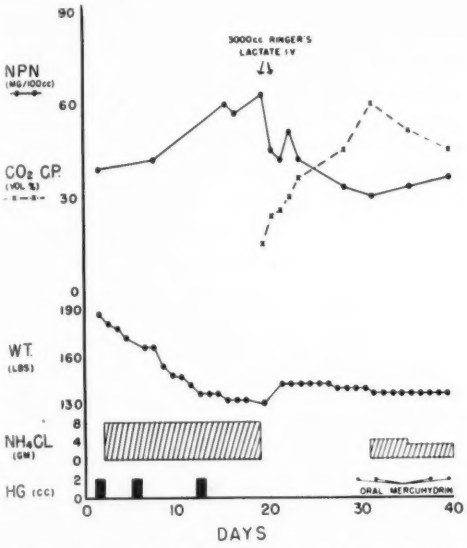

FIG. 4. The clinical course, ammonium chloride administration, and laboratory findings in J. R., case 6. Note the progressive rise in carbon dioxide combining power and fall in blood nonprotein nitrogen following omission of ammonium chloride therapy and after the intravenous administration of fluids.

The patient expired 15 months after discharge, following an episode of severe substernal pain. The autopsy findings included coronary arteriosclerosis, cardiac enlargement, calcific aortic and mitral stenosis, passive congestion of the lungs and viscera, and intercapillary glomerulosclerosis.

DISCUSSION

The common dosage schedule of ammonium chloride in congestive heart failure is 3 to 8 Gm. per day.[8, 10, 11] This amount is not sufficient to produce a significant degree of acidosis in a normal individual, and in our experience many patients with congestive heart failure without renal disease have taken 3 to 4 Gm. daily for long periods without any obvious untoward effects. Moreover, a review of the recent literature from 1935 to date has revealed no reports of serious ammonium chloride acidosis in patients with congestive heart failure.

Significant acidosis, however, has been produced in normal subjects by the administration of 15 Gm. of ammonium chloride per day for two days and 10 Gm. daily for the following three days.[12] Following the initial rise in plasma chloride and fall in bicarbonate, there occurs urinary loss of fixed base and water and lowering of blood pH.[12, 13] The acidotic state is accompanied by hyperventilation and increased cardiac work with increased oxygen consumption.[14] In normal individuals compensatory mechanisms exist which protect body base from further depletion and correct the acidosis. These are renal in nature and include increased urinary chloride resorption, despite increased chloride excretion, elaboration of a maximally acid urine (pH 4.4 to 4.7) and ammonia production by the renal tubules after an initial lag period of approximately 48 hours.

Previous studies [15, 16] have demonstrated, in patients with nephritis, impairment of renal capacity to excrete a maximally acid urine and to produce ammonia; there is a consequent loss of fixed base. The danger of administration of acid producing salts to patients with intrinsic renal disease has therefore been stressed. There is good evidence for the presence of intrinsic renal disease or impaired kidney function in all 6 patients reported here. In case 1 there was chronic cystitis and pyelonephritis secondary to prostatic obstruction, persistent marked albuminuria, low specific gravity and positive urine cultures for *Ps. aeruginosa*, *P. vulgaris* and *B. coli*. The long-standing diabetes mellitus, hypertension and 3 to 4 plus albuminuria in case 2 are consistent with vascular nephritis or intercapillary glomerulosclerosis. In case 3 there was persistent elevation of the blood nonprotein nitrogen and low fixed urinary specific gravity. Case 4 had subacute glomerulonephritis. In case 5 marked albuminuria, low fixed urine specific gravity and elevation of the blood nonprotein nitrogen was observed and, at postmortem examination during a sub-

sequent admission, chronic glomerulonephritis was demonstrated. Case 6 had long-standing diabetes, hypertension, albuminuria and, at postmortem examination during a subsequent admission, the kidneys showed the characteristic lesions of intercapillary glomerulosclerosis.

Relationship of Acidosis to Amount of Ammonium Chloride and Congestive Heart Failure

Each patient received 6 to 8 Gm. of ammonium chloride for 7 to 45 days. The degree of acidosis judged by clinical symptoms and by the fall in carbon dioxide combining power was not directly proportional to the amount of drug administered. Cases 4 and 6 received large amounts of ammonium chloride (278 and 136 Gm. respectively) over a long period of time and the consequent acidosis was not more severe than that observed in cases 1 and 2 who received considerably less (42 and 64 Gm.) over a shorter period of time. There was also no strict correlation between the severity of the acidosis and the degree of congestive heart failure at the outset of ammonium chloride therapy. In each instance at the time of occurrence of acidosis, moreover, an excellent diuretic response had already been obtained and cardiac compensation had largely been restored.

Relationship of Altered Renal Circulation of Congestive Heart Failure to Acidosis

In congestive heart failure the kidneys are enlarged as a result of venous engorgement and and dilatation of peritubular capillaries; microscopically there may be cloudy swelling.[17] The albuminuria, cylindruria, oliguria and mildly elevated blood nonprotein nitrogen commonly seen in patients with congestive failure are, however, reversible with the attainment of compensation and consequently have been felt to be functional in origin.

Studies of the renal circulation in patients with congestive failure have shown a decreased renal blood flow, a decreased glomerular filtration and an increased renal venous pressure. These changes are accompanied by retention of sodium and water.[18-25] When chloride is administered with sodium in patients with congestive heart failure, the chloride is retained in excessive amounts as sodium chloride.[18,25] However, in patients with congestive heart failure on a low-salt diet given chloride as ammonium chloride, Farnsworth[26] found that the ratio of sodium to chloride excreted was 0.40 as compared to 0.90 in normal subjects on the same regimen. These observations suggest that the kidney in congestive heart failure is not hampered in its excretion of chloride when this anion is administered without sodium.

The severe acidosis in the cases reported here is believed to be related to intrinsic renal disease and the inability of the kidneys to prevent continued loss through the urine of fixed base with chloride. The elevated plasma chloride concentrations observed in ammonium chloride acidosis are related to (1) continued intake of chloride, (2) increased tubular reabsorption of chlorides and (3) in part dehydration resulting from marked water loss.[12] A further effect of acidosis with its compensatory loss of base and water is a decrease in urea clearance and a rise in nonprotein nitrogen (cases 1, 3, 5, 6).[27]

Sufficient data is lacking to assess the role of the anemia observed in cases 3 and 5 in the production of acidosis. In each instance the anemia was severe, the hemoglobin value being 7 Gm. per hundred cc. It is known that the renal blood flow is considerably decreased in severe anemia, that sodium retention occurs and that there is impaired tubular function.[28-30] Because of the low hematocrit, however, plasma filtration is nearly normal and, hence, nitrogen retention is uncommon. We have been unable to find any studies of the effect of ammonium chloride on kidney function in the presence of anemia.

Data is absent concerning two other factors important in the elucidation of the acidosis observed in these patients. These include the question of impairment of ammonia formation by the renal tubules and the ability of the kidneys in congestive failure to secrete a maximally acid urine. These two factors may be important in the development of the acidosis reported here but, at this time, cannot be properly evaluated.

Clinical Picture of Ammonium Chloride Acidosis

Ammonium chloride acidosis, in the varying degrees observed in these patients, does not

differ clinically from acidosis of other states. Milder symptoms included anorexia, nausea and lassitude. In the more seriously ill patients, vomiting and progression of lassitude to marked stupor with Kussmaul respiration were observed. Since digestive complaints in patients receiving ammonium chloride are not uncommon, their onset may not be considered evidence of intoxication; however, it is noteworthy that 4 patients (cases 3, 4, 5, 6) had either nausea, vomiting or anorexia or combinations of all three as the initial manifestations of acidosis. Also, the systemic evidences of the acidosis appeared shortly after the gastrointestinal symptoms in 3 patients (cases 4, 5, 6) so that omission of the drug as well as administration of fluid and lactate intravenously were necessary to correct the acidosis. It should be emphasized that the onset of acidosis in 2 patients (cases 1 and 2) was marked by initial symptoms of drowsiness and apathy with rapid progression to marked stupor. Three other patients (cases 4, 5, 6) were drowsy and 3 patients (cases 2, 4, 5) exhibited Kussmaul respiration.

The presenting symptoms and signs in case 2 suggested a cerebrovascular accident. There was marked stupor, areflexia, and "blowing" expirations through one corner of the mouth. The chemical findings of acidosis and the response to therapy corrected this erroneous impression.

The azotemia seen in these patients was much more marked than that usually seen in patients with congestive failure, the blood nonprotein nitrogen (cases 1, 3, 5) ranging from 80 to 124 mg. per hundred cc. The clinical symptoms and the laboratory findings presented by these patients could be considered compatible with the diagnosis of uremia; however, the drop in nonprotein nitrogen following omission of ammonium chloride and administration of alkali would indicate that true uremia had not been present.

Since 2 of the patients (cases 2 and 6) were diabetic it was important to exclude diabetic acidosis. This was readily accomplished in these 2 patients by the absence of glycosuria and acetonuria.

The occurrence of drowsiness, weakness, lethargy, nausea and vomiting following vigorous use of mercurial diuretics suggests the "low salt syndrome" seen in patients with congestive heart failure and diminished renal function. Further similarities to the cases observed by us include a rising and high nonprotein nitrogen. Acidosis is, however, not observed in the low salt syndrome and plasma sodium and chloride are markedly depleted in contrast to the high chlorides found in the cases observed by us. Furthermore, in only one patient (case 1) was there observed a reduction in urinary output during the period of ammonium chloride acidosis; in the cases described by Schroeder[31] marked oliguria and in some instances anuria were witnessed. None of the patients described in this report demonstrated gain in weight during the period of acidosis in contrast to the common occurrence of rapid and progressive gain in weight observed in the "low salt syndrome." Muscular cramps, furthermore, common occurrences following diuresis and marked depletion of sodium chloride, were not observed in our cases.

Although ammonium chloride is a valuable adjunct in the management of congestive heart failure, it should be used with great caution when renal disease is suspected or is present. The demonstration of organic renal disease in patients with congestive heart failure may be difficult; functional impairment as witnessed by albuminuria, oliguria and mildly elevated blood nonprotein nitrogen are common. Marked, persistent albuminuria (cases 1, 2, 4, 5, 6) and low fixed specific gravity (cases 1, 3, 5) in patients with congestive heart failure are, however, indicative of intrinsic renal disease. The finding of a blood nonprotein nitrogen level above 60 to 70 mg. per hundred cc. in a patient with congestive heart failure should raise the possibility of intrinsic renal disease; in such patients, caution must be exercised in the administration of ammonium chloride. The presence of persistent albuminuria and cellular elements after clearing of congestive failure (cases 1, 2, 3, 5, 6) should raise the suspicion of intrinsic renal disease. It is suggested, on the basis of the observations presented here, that the administration of ammonium chloride in such instances be limited to a period of

three consecutive days per week. When longer periods of administration are necessary, careful observation of the patient and measurement of the carbon dioxide combining power are indicated.

Summary

1. Ammonium chloride acidosis, observed in 6 patients, has been described. The acidosis was severe in 4 cases and nearly fatal in 2. Six to 8 Gm. were administered to each patient for 7 to 45 days. Five patients had congestive heart failure and one, subacute glomerulonephritis. Each of the 5 patients with congestive failure had underlying renal disease. The clinical manifestations ranged from anorexia, nausea and vomiting with lassitude to marked stupor, areflexia and Kussmaul respiration. In all cases rapid improvement followed omission of ammonium chloride and administration of fluids and lactate intravenously.

2. No close relationship between the degree of congestive heart failure, the amount of drug administered or the severity of acidosis was noted. Three of the patients in congestive heart failure developed marked azotemia.

3. The possible roles of altered renal hemodynamics in congestive heart failure and anemia in the etiology of the acidosis is discussed.

4. Ammonium chloride is a valuable adjunct in the management of congestive heart failure, but should be used with great caution when renal disease is suspected or present. It is suggested that the administration of ammonium chloride be limited to a period of three consecutive days per week. When longer periods of administration are necessary, careful observation of the patient and measurement of the carbon dioxide combining power are indicated.

REFERENCES

[1] Gamble, J. L., Blackfan, K. D., and Hamilton, B.: A study of the diuretic action of acid producing salts. J. Clin. Investigation **1:** 359, 1924–1925.

[2] Keith, N. M., and Whalen, M.: A study of the action of ammonium chloride and organic mercury compounds. J. Clin. Investigation **3:** 149, 1926–1927.

[3] Blumgart, H. L., Gilligan, D. R., and Volk, M. C.: The action of diuretic drugs. II. Effect of diuretic drugs on the acid-base equilibrium of blood in patients with cardiac disease. Medical Papers Dedicated to Henry Asbury Christian. Baltimore, Waverly Press, Inc., 1936. P. 193.

[4] Keith, N. M., Barrier, C. W., and Whalen, M.: Diuretic action of ammonium chloride and novasurol. J. A. M. A. **85:** 779, 1925.

[5] Goodman, L., and Gilman, A.: The pharmacological basis of therapeutics. The Macmillan Company, New York, 1941. P. 631.

[6] Stroud, W. D.: The Diagnosis and Treatment of Cardiovascular Disease, Vol. II. Philadelphia, F. A. Davis Company, 1940. P. 1815.

[7] Fishberg, A. M.: Hypertension and Nephritis, ed. 4. Philadelphia, Lea and Febiger, 1948. P. 152.

[8] Friedberg, C. K.: Diseases of the Heart. Philadelphia, W. B. Saunders Co., 1949. P. 200.

[9] Talkov, R. H., Ropes, M. W., and Bauer, W.: The value of enteric coated aspirin. New England J. Med. **242:** 19, 1950.

[10] White, P. D.: Heart Disease, ed. 3. New York, The Macmillan Co., 1946. P. 784.

[11] Levine, S. A.: Clinical Heart Disease, ed. 3. Philadelphia, W. B. Saunders Company, 1945. P. 279.

[12] Sartorius, O. W., Roemmelt, J. C., and Pitts, R. F.: The renal regulation and acid-base balance in man. IV. Nature of renal compensations in ammonium chloride acidosis. J. Clin. Investigation **28:** 423, 1949.

[13] Folling, A.: On the mechanism of ammonium chloride acidosis. Acta med. Scandinav. **41:** 221, 1929.

[14] Altschule, M. D.: Physiology in Diseases of the Heart and Lungs. Harvard University Monograph in Medicine and Public Health, No. 10. Cambridge, Harvard University Press, 1949. Pp. 193–194.

[15] Henderson, L. J., and Palmer, W. W.: On the several factors of acid excretion in nephritis. J. Biol. Chem. **21:** 37, 1915.

[16] Van Slyke, D. D., Linder, G. C., Hiller, A., Leiter, L., and McIntosh, J. F.: The excretion of ammonia and titratable acid in nephritis. J. Clin. Investigation **2:** 255, 1925–1926.

[17] Bradley, S. E., and Blake, W. D.: Pathogenesis of renal dysfunction during congestive heart failure. Am. J. Med. **6:** 470, 1949.

[18] Futcher, P. H., and Schroeder, H. A.: Studies on congestive heart failure. II. Impaired renal excretion of sodium chloride. Am. J. M. Sc. **204:** 52, 1942.

[19] Seymour, W. B., Pritchard, W. H., Langley, L. P., and Hayman, J. M., Jr.: Cardiac output, blood and interstitial fluid volumes, total circulating serum protein and kidney function during cardiac failure and after improvement. J. Clin. Investigation **21:** 229, 1942.

[20] Warren, J. V., and Stead, E. A., Jr.: Fluid

dynamics in chronic congestive heart failure. An interpretation of the mechanisms producing the edema, increased plasma volume and elevated venous pressure in certain patients with prolonged congestive heart failure. Arch. Int. Med. **73:** 138, 1944.

[21] MERRILL, A. J.: Edema and decreased renal blood flow in patients with chronic congestive heart failure: evidence of "forward failure" as the primary cause of edema. J. Clin. Investigation **25:** 389, 1946.

[22] REASER, P. B., AND BURCH, G. E.: Radiosodium tracer studies in congestive heart failure. Proc. Soc. Exper. Biol. & Med. **63:** 543, 1946.

[23] MOKOTOFF, R., ROSS, G., AND LEITER, L.: Renal plasma flow and sodium resorption and excretion in congestive heart failure. J. Clin. Investigation **27:** 1, 1948.

[24] SMITH-SMITH, B., KATTUS, A. A., GENEST, J., AND NEWMAN, E. V.: Changes in the renal mechanism of electrolyte excretion and the metabolic balances of electrolytes and nitrogen in congestive cardiac failure with exercise, rest and aminophyllin. Bull. Johns Hopkins Hosp. **84:** 369, 1949.

[25] SCHROEDER, H.: Studies in congestive circulatory failure. III. The relation of edema to urinary chlorides. Circulation **1:** 481, 1950.

[26] FARNSWORTH, E. B.: Electrolyte partition in patients with edema of various origins. Sodium and chloride. Am. J. Med. **4:** 338, 1948.

[27] MCCANCE, R. A., AND LAWRENCE, R. D.: The secretion of urine in diabetic coma. Quart. J. Med. **4:** 53, 1935.

[28] BLUMGART, H. L., AND ALTSHULE, M. D.: Clinical significance of cardiac and respiratory adjustments in chronic anemia. Blood **3:** 329, 1948.

[29] STRAUSS, M. B., AND FOX, H. J.: Anemia and water retention. Am. J. M. Sc. **200:** 454, 1940.

[30] BRADLEY, S. E., AND BRADLEY, G. P.: Renal function during chronic anemia in man. Blood **2:** 192, 1947.

[31] SCHROEDER, H. A.: Renal failure associated with low extracellular sodium chloride. The low salt syndrome. J. A. M. A. **141:** 117, 1949.

The Heart in Progressive Muscular Dystrophy

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A case of progressive muscular dystrophy with cardiac involvement in a young Negro man is reported. The presenting problem was cardiomegaly and congestive heart failure. It was not until compensation was achieved that the underlying myopathy became apparent. Death was unexpected and presumably sudden. An unusual finding at the postmortem examination was the marked thickening of the endocardium. The literature in regard to the clinical and pathologic manifestations of cardiac involvement in this myopathy is reviewed.

ORDINARILY, the presence of heart failure is readily recognized. However, the nature of the underlying disease affecting the heart is often not discernible. Recently, we were confonted with the problem of heart failure in a patient who was presumed to have "idiopathic cardiomegaly." It was not until cardiac compensation was achieved that the nature of the underlying disease, namely, progressive muscular dystrophy, became apparent.

This paper emphasizes the occurrence of cardiac involvement in progressive muscular dystrophy by (1) reporting case and (2) reviewing the literature in regard to the cardiac manifestations in this myopathy.

CASE REPORT

L. L., a 30 year old Negro man, was referred to the Temple University Hospital because of increasing shortness of breath and swelling of the ankles. About one and one-half years ago, he began to experience easy fatigability and nocturnal attacks of shortness of breath. Occasionally, he complained of palpitation and painful sensations around the heart. Digitalis was prescribed by his physician one year ago. He took the drug at irregular intervals thereafter. During the past month, he noticed swelling of his ankles and increasing shortness of breath.

Systematic inquiry revealed that at the age of 13, he was seen in the Temple University Outpatient Cardiac Clinic because of pain in the ankle joints. Unfortunately, his record contained only an electrocardiogram which presented no abnormality. At the age of 21, during a routine pre-enlistment Army examination, he was told that he had a "leaky" heart and was advised to limit his activities. Since then, he had worked part-time as an attendant at a baseball park. Several years ago, he was told that he had high blood pressure.

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Physical examination revealed a well developed Negro man appearing younger than his stated age. He was exceedingly apprehensive, manifesting outspoken fright. Dyspnea, orthopnea, and cervical venous distention were present. Repeated determinations of the blood pressure varied from 100–150/70–112. The ocular fundi were normal. The point of maximal impulse was in the sixth intercostal space at the left midaxillary line. Cardiac dullness extended 7 cm. to the right of the midsternal line in the fourth intercostal space and 9 cm. to the left of the midsternal line in the third intercostal space. The ventricular rate was 120 per minute with a pulse deficit of 20 per minute. There was usually an irregular rhythm. Occasionally, a rapid regular rhythm with frequent extrasystoles occurred. The mitral first sound was decreased in intensity and the pulmonary second sound was accentuated. In the left lateral recumbent position, a soft low-pitched systolic murmur replacing the mitral first sound was audible. Examination of the lungs revealed dullness over the right lower lobe with decreased breath and voice sounds and bilateral basilar subcrepitant rales. The liver was palpated 4 cm. below the right costal cage and was not tender. Pitting edema of the legs was present. The usual therapeutic regimen employed in the management of congestive heart failure was instituted.

Following subsidence of the edema, it was noticed that his calf and arm muscles were unusually prominent. When allowed to ambulate, his gait was observed to be awkward, hesitant, and jerky. Upon arising from a sitting position on the floor, he would climb up his legs. There was weakness of the muscles in spite of their prominence. Neurologic consultation (Dr. S. F. Gilpin, Jr.) supported the diagnosis of progressive muscular dystrophy. This was confirmed by a right gastrocnemius muscle biopsy (fig. 1).

Examination of a 24 hour urine specimen revealed 774 mg. creatinine and 367 mg. creatine. Other laboratory studies disclosed a normal complete blood count and blood urea nitrogen and a negative serology. The sedimentation rate was 13 mm. in one hour. Repeated urinalyses disclosed the presence of proteinuria with hyaline and granular casts. The specific gravity of the urine varied from 1.010 to 1.025.

An electrocardiogram was taken on two occasions, one a day after admission, the other nine days later. Both were essentially similar. The later tracing is shown in figure 2. There is a sinus tachycardia at a rate of 116 per minute with occasional premature ventricular contractions. There is evidence of auricular disease and clockwise rotation of the heart around its long axis with left ventricular hypertrophy.

Roentgenographic examination of the chest (figure 3) revealed increased bronchovascular markings of central distribution indicating pulmonary congestion. There was marked enlargement of the heart, predominantly of the left ventricle. Left auricular enlargement was demonstrated by the double shadow within the right heart border and by displacement of the barium-filled esophagus.

Clinically, the patient was responding satisfactorily to treatment. Arrangements were being made for his discharge. Early one morning, 19 days after admission, the patient was found dead by a nurse on her routine ward rounds.

Autopsy Findings

Gross examination of the gastrocnemius and related calf muscles showed them to be flabby, yellow and greasy. Compared with these muscles, those of the thigh, trunk and arm appeared normally red and of decidedly better tone. It is of interest that the stomach contained approximately 200 cc. of fresh blood. Three of the 4 cases reported by Bevan also had gastric bleeding. Our case had neither frank ulcers nor perforations.

From a survey, both gross and microscopic, of the tissues after death, it seems probable that the patient died of sudden cardiac arrest. All sections showed the effect of longstanding congestion with a terminal acute exacerbation. In addition there were antemortem thrombi in both auricles and old and recent infarcts in the spleen and in both kidneys, dramatic proof that the cardiac injury was old.

The appearance of the heart itself was of greatest interest. It was enlarged by both dilatation and hypertrophy and both sides were about equally

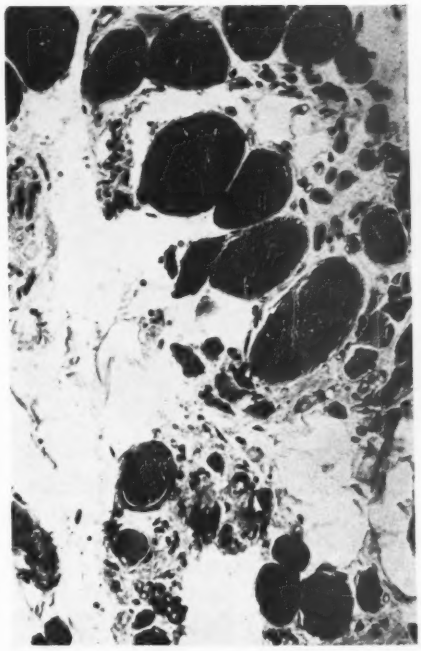

FIG. 1. Photomicrograph of skeletal muscle in cross section (220 ×). Most of the fibers reveal extreme hypertrophy. Interspersed are the very small, atrophic or hypogenetic fibers.

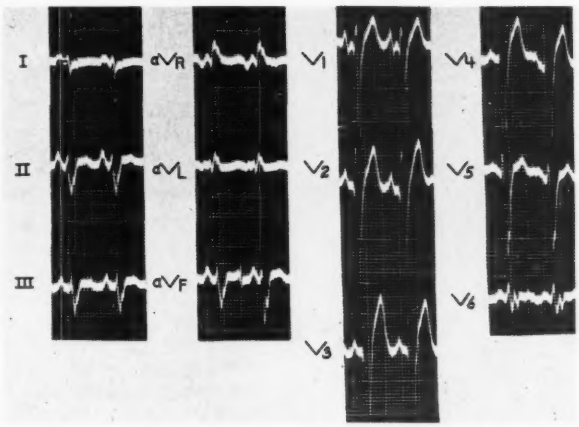

FIG. 2. Electrocardiogram (1/21/50) revealing auricular disease and clockwise rotation of the heart around its long axis with left ventricular hypertrophy.

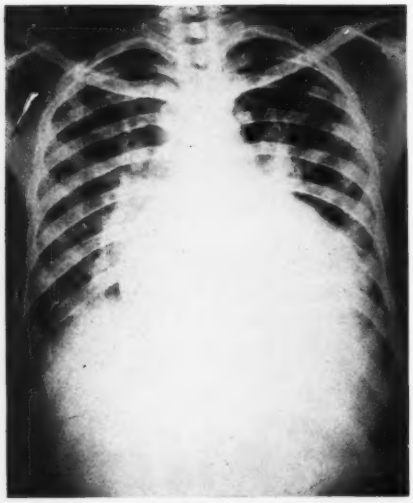

FIG. 3. Chest x-ray (1/13/50) showing pulmonary congestion and marked cardiac enlargement predominantly of the left ventricle.

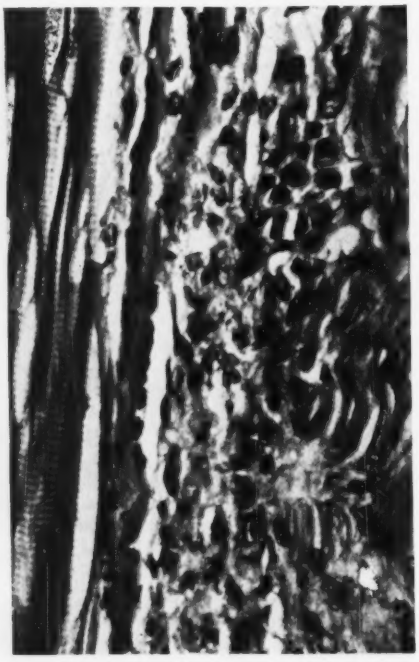

FIG. 4. Photomicrograph of heart muscle in longitudinal section (440 ×) . There is degeneration with an attempt at regeneration manifested by nuclear hyperplasia.

involved. The heart weighed 650 Gm. The wall of the left ventricle measured 2 cm. in its thickest area. The linings of the pericardial cavity were normal in appearance. The coronary vessels were without evidence of atherosclerosis and they were of normal size and pattern. There was no evidence that the changes found in the myocardium were due to a deficient blood supply. The myocardium of both

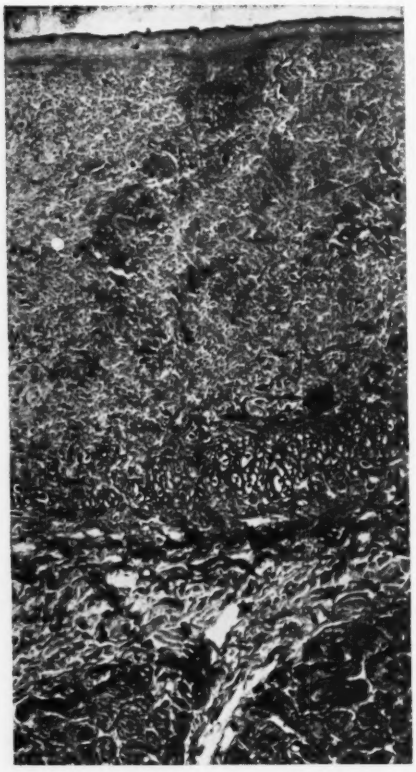

FIG. 5. Photomicrograph of section through inner layers of left ventricular wall (180 ×). The endocardium is many times thicker than normal. It is fibrous.

ventricles was firm and tough. When sectioned tangentially it was found to be laced and mottled with fine, gray striae and patches which resembled fibrous tissue. There were no delineated areas suggesting infarction. The left ventricular cavity was lined by a layer of smooth, yellowish-gray tissue measuring up to 1 mm. in thickness. The appearance was somewhat similar to that of fetal endocarditis. Three of Bevan's cases showed this same alteration. There was a smooth thickening of the distal edges of the leaflets of both mitral and tricuspid valves, but the appearance was not characteristic of that of

healed rheumatic valvulitis nor was the process extensive enough to cause a major disturbance in valve efficiency. The tricuspid valve ring was relaxed, measuring 14 cm. in circumference. The aortic valve ring circumference was less than normal, measuring 5 cm. This, coupled with the thickened endocardium, made one think of the possible relationship of this condition to fetal endocarditis in which the same cardiac lesions are sometimes found.

On microscopic examination the changes in the skeletal muscles were definite but not so severe nor so extensive as those of most cases of pseudohypertrophic muscular dystrophy. Giant hypertrophied fibers were occasionally found and there were scattered small areas in which the fibers had atrophied to approximately one fourth their normal size. Striations were quite sharply and clearly delineated as one expects them to be in this condition but there were focal condensations of sarcoplasm. Sarcolemmal nuclear proliferation was striking in some areas. The sections contained an abnormal amount of adult fat.

The changes in the myocardium were much more striking than those in the skeletal muscle. Here there were areas of recent degenerative change with accompanying exudative inflammatory reaction (fig. 4). There were irregular lines and patches of fibrous tissue through every section and almost every field. There was little, if any, excess fat in the myocardium. The striations were blurred and fuzzy. The endocardium and valve leaflets were considerably thickened by masses of collagenous tissues which were relatively acellular (fig. 5). Stains for elasticum showed little change in amount or distribution of that substance.

Discussion

When confronted with cardiomegaly, one ordinarily thinks of hypertensive, valvular, or congenital heart disease. Rarer causes include primary amyloidosis, glycogenosis, and beriberi. However, there are many of these cases for which no etiologic factor is, at present, apparent. These constitute the group known as "idiopathic cardiomegaly." The recent literature attests to the frequency with which this diagnosis is being made.[1, 2] With increasing knowledge, many cases will be separated from this group, as has recently been done by Evans.[3] Our patient had cardiomegaly and congestive heart failure. It was not until he was compensated and allowed to ambulate that the nature of the underlying disease became apparent.

Progressive muscular dystrophy usually develops in infancy or early childhood but may arise at any time from birth to adult life.[4–7] The earlier the onset, the more rapid the clinical course.[8] Males are more frequently affected than females.[8] Cases in Negroes have been described.[9–11] It is a disease affecting all types of muscle tissue.[12] In addition, there may be changes in the skin, bone, and endocrine glands.[12–14] Involvement of the skeletal muscle, however, results in the prominent and well known manifestations of this disease.[12, 15, 16]

The incidence of cardiac involvement in progressive muscular dystrophy is not known. In fact, in none of the modern texts nor in the recent literature has there been an attempt to estimate the incidence of the disease per se. In 1931, Hough[17] roughly estimated the incidence of this myopathy as being approximately 6 per 100,000 population. Meerwein[18] collected 480 cases of progressive muscular dystrophy published before 1904. In 89 of these, there was noted some abnormality of the heart or pulse. In our review, with particular emphasis on the literature since Globus' report in 1922,[19] we have encountered a total of 292 cases. In 156 of these, nothing was stated in regard to the cardiovascular system. In 42 cases, whatever cardiovascular data were presented (usually meager) were normal. In 94 cases, whatever cardiovascular data were presented, whether clinical, radiologic, electrocardiographic, or postmortem, were abnormal. These figures are cited only to indicate the fact that the cardiovascular system is involved in progressive muscular dystrophy in a considerable percentage of cases. A more specific conclusion cannot be made from these data because, first, our interest was directed particularly to cardiovascular abnormalities, and second, cases are usually reported in a manner dependent upon the interest of the observer. It should be noted that in cursory observations by previous workers, opinions as to the incidence of cardiac involvement in this myopathy have varied from one of doubt as to its very occurrence to one in which it was thought to be present sooner or later in every case.[20, 21]

The most prominent symptoms of cardiac involvement in progressive muscular dystrophy

appear to be related to the arrhythmias which frequently occur in these patients. They may be perfectly well and then suddenly feel sick, experience palpitation, and then break out in a cold sweat, accompanied at times by vomiting and abdominal pain. Not infrequently, there may be a sudden shock-like state, either without apparent cause or following minor stimuli, terminating equally abruptly either in recovery or death. Gastrointestinal complaints may occasionally predominate to a degree warranting an exploratory laparotomy.[9, 22] In one such instance, death occurred postoperatively, presumably as a result of a cardiac arrhythmia.[23] There may be recurrent bouts of fever and tachycardia, with or without gastrointestinal symptoms.[23] The daily variations in the temperature curve may be exaggerated.[23] A few may be dyspneic.[10] Swelling of the legs was rarely noted. Two patients had precordial pain.[24, 25] It is to be emphasized that some of these patients offer no complaints until the attending physician, faced with electrocardiographic evidence of an arrhythmia as the sole evidence of heart disease, inquires and discovers that periodic palpitations have been frequently experienced.[26]

A statement in regard to the clinical evaluation of heart size was noted in 38 instances. In 6 of these the heart was found to be enlarged.[9, 12, 25, 27, 28] The sounds were usually of good quality. Hurwitz[30] observed a slurred first heart sound and Boas and Lowenburg[18] emphasized the presence of a feeble first heart sound at the apex and an accentuated second sound at the base. Bert and Barati[24] heard an opening snap with duplication of the first heart sound, confirmed by phonocardiography. Murmurs were present in a few instances.[9, 18, 25, 27, 31] These were usually systolic in time and soft in character, located at the apex or base of the heart. In a case of Bevan's,[9] the murmur was harsh. Two patients had rheumatic heart disease and mitral stenosis.[25, 26] In one instance, a gallop rhythm was intermittently present.[9] In 2 patients with precordial pain, auscultation revealed a pericardial friction rub in one,[3] and mitral stenosis in the other.[25]

The blood pressure was recorded in only 24 instances. In 10 patients either the systolic or diastolic or both were elevated.[9, 10, 12, 18, 24, 32–34] Another patient, a 24 year old male, had a past history of hypertension.[27] Of these 11 patients, 7 were below the age of 40 years. In 5 patients, 10 years of age or less, the blood pressure was within normal limits. In the remaining patients, the blood pressure ranged from 100–130/50–84. Funduscopic examination was done in 7 cases,[12, 27, 28, 29] being normal in 6 of these. In the patient who had a history of hypertension, the retinal arterioles were narrowed.[27] In view of these data, it is remarkable that some have regarded a hypotensive state as an almost constant finding.[24]

Boas and Lowenburg[18] studied the heart rate of 7 patients with progressive muscular dystrophy by means of a cardiotachometer. The striking feature noted was the tachycardia evident in each of these patients both waking and sleeping. The absence of the normal drop in pulse rate during sleep was confirmed by Kraus.[35] Another characteristic finding was the lability of the heart rate, accelerating excessively in response to minimal stimuli.[18]

In our review, a notation regarding the clinical rate or rhythm was found in 27 instances.[9, 18, 20, 22–26, 28, 33, 36, 37] The rate was recorded in 12 and varied from 80 to 180 per minute. A few of those with the slower rates had periods during which the pulse rate was increased.[9, 22, 23, 25] In 8 patients there was observed either an irregular pulse or periods of rapid heart action. In one of the patients, the pulse suddenly became irregular at a rate of 160 per minute.[23] Pressure on the "right vagus" resulted in a temporary cessation of this arrhythmia. Interestingly, the sudden onset of these rapid arrhythmias was often related to minor stimuli, such as a scolding[22] or a tooth extraction.[19]

The results of x-ray examination of the heart were noted in 25 instances.[9, 18, 24, 27, 36, 38, 39] The examination was negative in 15 of these.[9, 18, 24, 36, 38] In one, the size of the heart was indeterminate[9]; in another, the cardiac silhouette was "ball-shaped."[38] In the others, the heart was found to be enlarged, either slightly or in all diameters. In one patient, the esopha-

gus was slightly displaced by an enlarged right auricle.[9] A kymographic study was done in this patient and small excursions were observed.

Electrocardiographic observations were recorded in 105 instances. The rate was usually rapid with normal or irregular sinus rhythm (sinus arrhythmia). Extrasystoles, either auricular or ventricular in origin, were not infreuent. In one patient, ventricular extrasystoles occurred in bigeminy.[22] Two had paroxysmal ventricular tachycardia.[22, 23] The P wave was of increased amplitude in leads II and III in a patient with progressive muscular dystrophy who also had rheumatic heart disease and mitral stenosis.[26] In another, the P wave was 4 mm. in amplitude in lead II.[38] The P-R interval was normal in all but 3 cases.[24, 26] In 2, the P-R interval was longer than 0.20 second [24, 26]; in another, a Wolff-Parkinson-White syndrome was present.[26] The duration of the QRS complex was prolonged in 3.[22, 27, 32] Lengthening of the Q-T interval was observed once.[39]

As is true of the early electrocardiographic literature, much emphasis was placed on the configuration of the QRS complex in the limb leads. The mean electrical axis of the QRS complex was usually normal, occasionally deviated either to the right or to the left.[26] A Q wave was frequently found, particularly in leads II and III.[38] These were carefully compared with the Q wave of Pardee, the author concluding that they probably denoted myocardial involvement not otherwise apparent.[38] There was not one instance of an abnormally wide Q wave. In one patient, after the development of precordial pain accompanied by a friction rub, the Q wave in lead I increased.[24] The R wave was frequently of increased voltage in leads I and II, and low or absent in lead III.[24, 38] Occasionally, it was notched, slurred, or thickened.[24] The S-T interval was often abbreviated, there being an early takeoff of T.[38] Occasionally, the S-T segment was slightly elevated in the limb leads, particularly in leads I and II; infrequently, it was slightly depressed in lead III.[24, 38]

In leads I and II, the T wave was usually upright, occasionally quite tall and peaked, rarely low positive. The T wave in lead III was frequently flattened or inverted.[38] In the one study in which it was stated that precordial leads were employed, CF_3 and IV_F were chosen.[26] These revealed nothing of note.

Globus,[19] in a review of the literature to 1922, summarized the postmortem findings of the heart in 10 cases of progressive muscular dystrophy and reported an additional case. He was particularly interested in determining the relationship of the heart changes in this myopathy to a possible acute intercurrent disease or to some past illness. All showed fairly definite myocardial disease of varying degree. He concluded that infection was insufficient to explain the diffuse nature and the morphologic character of the myocardial involvement.

In a review of the literature since 1922, we were able to find 19 additional cases in which necropsies were done and reported in whole or in part. The ages at death varied from 10 years to 67 years, the average being 25.4 years. All but one were males.

Death occurred suddenly in 2 cases,[40] within 35 minutes in another,[32] within three hours in 1,[20] within 48 hours in 2,[27, 32] and on the second to fourth postoperative day in 3.[9, 32, 33] The two deaths which occurred suddenly were attributed to "edema of the larynx—status lymphaticus."[40] Twelve patients died shortly after development of a respiratory infection. In one, death followed respiratory paralysis.[32] One died of acute left ventricular failure.[32] In one, "disturbances of the heart" developed, resulting in the patient's death.[21] Another died during a bout of diarrhea, fever, and tachycardia of 180 beats per minute.[9]

The weight of the heart was recorded in 7 instances and varied from 140 Gm. to 600 Gm., four hearts weighing 190 Gm. or less,[9, 41] and three weighing 285 Gm. or more.[9, 20, 27] In an additional case, it is stated that the heart was hypertrophied.[32] In 4, there was dilatation;[21, 40, 41] and, in one, a striking bulge of the left ventricle was observed.[42]

The epicardial fat was increased in some and, at times, found to "invade" the myocardium. Occasionally, areas of heart muscle were replaced by connective tissue. The ventricular

wall was usually streaked with greyish flecks and small fibrotic areas were frequently recognized. The muscle tone was usually increased; occasionally, the wall was flabby. The endocardium grossly was normal or slightly thickened. Mural thrombi were observed in only one case.[27] The valves were not involved. The coronary blood vessels were patent in all but one.[32] The latter, a 61 year old male, had extensive arteriosclerosis with old occlusions of both branches of the left coronary artery.

Microscopically, fibrosis of the myocardium was observed, varying from a finely diffuse sclerosis to large areas of scarring. There was usually fatty infiltration and edema not only of the interstitial tissue but also of the muscle. The muscle fibers varied in size. In some instances they had undergone degeneration and were replaced by connective tissue. There was fragmentation, loss of striation, and condensation of cytoplasm. The nuclei showed degenerative changes. In some cases there was a diffuse but sparse infiltration of the myocardium with wandering cells and histiocytes. No evidence of a specific inflammatory reaction was present. The endocardium, microscopically, was usually normal; occasionally, it was found to be slightly thickened in a few small areas.

An unusual feature in our case was the thickening of the endocardium. Idiopathic hypertrophy of the heart with endocardial fibrosis has been reported in infants.[43] According to Kugel and Stoloff,[44] the true form of idiopathic congenital cardiac hypertrophy reveals no myocardial fibrosis. Weisman[45] has reported 2 such cases. In Mahon's case,[46] there were fibrotic and degenerative myocardial changes, but associated lesions were present to suggest an inflammatory origin.

The various changes in the reported cases were more extensive in the left ventricle than in the right. Although the coronary vessels were usually free of disease, a few observers noted small intimal atheromas.[9, 20] These were sometimes found in the aorta also.[9] The aorta was occasionally found to be smaller than normal.[27] Thromboembolic disease was observed in 3 instances.[7, 27, 32] Chronic passive congestion was infrequently noted, owing probably to the early demise of these patients.

As has been emphasized by others, more of these cases will be recognized if a sense of awareness is maintained. The peculiar gait, large calves, and "climbing up the legs" (Gower's sign) constitute an important triad in the diagnosis of progressive muscular dystrophy. A labile and rapid pulse rate, an arrhythmia, or an abnormal character of the heart sounds suggest cardiac involvement, which may be confirmed by electrocardiographic study.

Summary

The occurrence of cardiac involvement in progressive muscular dystrophy is emphasized by (1) reporting a case of a young Negro man with cardiomegaly in whom the underlying myopathy was masked by heart failure and (2) summarizing the literature in regard to the clinical, electrocardiographic, radiographic, and pathologic manifestations.

REFERENCES

1 Levy, R. L., and von Glahn, W. C.: Cardiac hypertrophy of unknown cause. A study of the clinical and pathologic features in ten adults. Am. Heart J. **28:** 714, 1944.

2 Norris, R. F., and Siegler, A. M.: Hypertrophy of the heart of unknown cause in young adults. Report of two additional cases. U. S. Nav. M. Bull. **49:** 523, 1949.

3 Evans, W.: Familial cardiomegaly. Brit. Heart J. **11:** 68, 1949.

4 Funsten, R. V.: A clinical study of thirty cases of muscular dystrophy. J. Bone & Joint Surg. **5:** 190, 1923.

5 Summers, V. K.: Pseudo-hypertrophic muscular dystrophy. Brit. M. J. **1:** 850, 1947.

6 Blalock, T. F.: Progressive muscular dystrophy. Report of a case. U. S. Nav. M. Bull. **43:** 129, 1944.

7 Milhorat, A. I., and Wolff, H. G.: Studies in diseases of muscle. XIII. Progressive muscular dystrophy of atrophic distal type; report on a family; report of autopsy. Arch. Neurol. & Psychiat. **49:** 655, 1943.

8 —, and —: Studies in diseases of muscle. XII. Heredity of progressive muscular dystrophy; relationship between age at onset of symptoms and clinical course. Arch. Neurol. & Psychiat. **49:** 641, 1943.

9 Bevan, M.: Changes in the musculature of the gastrointestinal tract and in the myocardium in progressive muscular dystrophy. Arch. Path. **40:** 225, 1945.

10 Howser, J. P.: Pseudohypertrophic myopathy

in a Negro adult. M. Bull. Vet. Adm. **20:** 97, 1943.

[11] Lowe, R. C.: Polycythemia vera (erythemia), arachnodactyl with congenital defect of the vertebral column, and familial muscular dystrophy in negroes. Case Reports. Tri-State M. J. **13:** 2679, 1941.

[12] Bramwell, E.: The muscular dystrophies, sympathetic system, and endocrine glands. Lancet **209:** 1103, 1925.

[13] Berman, L.: Progressive muscular dystrophy. A biochemical endocrine study. New York State J. Med. **37:** 1191, 1937.

[14] Janney, N. W., Goodhart, S. P., and Isaacson, V. I.: The endocrine origin of muscular dystrophy. Arch. Int. Med. **21:** 188, 1918.

[15] Bowden, R. E. M., and Gutmann, E.: Observations in a case of muscular dystrophy with reference to diagnostic significance. Arch. Neurol. & Psychiat. **56:** 1, 1946.

[16] Hassin, G. B.: Histopathology of progressive muscular dystrophy. J. Neuropath. & Exper. Neurol. **2:** 315, 1943.

[17] Hough, G. DeK., Jr.: Progressive pseudohypertrophic muscular dystrophy. Report of results of treatment with adrenalin and pilocarpin with an analysis of 28 cases. J. Bone & Joint Surg. **13:** 825, 1931.

[18] Boas, E. P., and Lowenburg, H.: The heart rate in progressive muscular dystrophy. Studies with the cardiotachometer. Arch. Int. Med. **47:** 374, 1931.

[19] Globus, J. H.: The pathologic findings in the heart muscle in progressive muscular dystrophy. Arch. Neurol & Psychiat. **9:** 59, 1923.

[20] Cohen, S.: Myocardial fibrosis in progressive muscular dystrophy. J. Med. **17:** 26, 1936.

[21] Meyenburg, H. V.: Ueber die Bedeutung der Myokarderkrankung bei der progressiven Muskeldystrophie. Schweiz. med. Wchnschr. **65:** 217, 1935.

[22] Schliephake, E.: Der Kardio-intestinale Symptomenkomplex bei der progressiven Muskeldystrophie. II. Mitteilung. Graphische Untersuchungen. Ztschr. f. Kinderh. **47:** 85, 1929.

[23] Berblinger, Prof. Dr., and Duken, Prof. Dr.: Der Kardio-intestinale Symptomenkomplex bei der progressiven Muskeldystrophie. I. Mittelung. Klinische und pathologisch-anatomische Beobachtungen. Ztchr. f. Kinderh. **47:** 1, 1929.

[24] Bert, J. M., and Barati, H.: Le coeur dans les myopathies. Montpellier méd. **21–22:** 13, 1942.

[25] Wiltschur, O. M.: Pathogenesis and therapy of progressive muscular dystrophy with primary involvement of heart muscle. Sovet. klin. **20:** 61, 1934.

[26] Puddu, V., and Safia, A. Mu.: L'électrocardiogramme dans la dystrophie musculaire progressive. Arch. d. mal. du coeur. **32:** 958, 1939.

[27] Case Presentation (#33311). New England J. Med. **237:** 163, 1947.

[28] Lawrence, B. G.: Pseudo-hypertrophic muscular dystrophy in brother and sister. Delaware State M. J. **6:** 108, 1934.

[29] Byard, D. S.: Four cases of muscular dystrophy. Internat. Clin. **1:** 174, 1923.

[30] Hurwitz, S.: Primary myopathies. Report of 36 cases and review of the literature. Arch. Neurol. & Psychiat. **36:** 1294, 1936.

[31] Pi, C. C.: Pseudohypertrophic muscular dystrophy. Report of two cases in Chinese children. Chinese M. J. **49:** 1306, 1935.

[32] Goodhart, S. P.: Progressive muscular dystrophies. Necropsy studies in four cases. J. Mt. Sinai Hosp. **9:** 514, 1942–1943.

[33] Conwell, D. V.: Remissions in progressive muscular dystrophy. J. Kansas M. Soc. **37:** 221, 1936.

[34] Nevin, S.: Two cases of muscular degeneration occurring in late adult life with a review of the recorded cases of late progressive muscular dystrophy (late progressive myopathy). Quart. J. Med. **5:** 51, 1936.

[35] Kraus, W. M.: The pulse curve in a case of progressive muscular dystrophy. Arch. Neurol. & Psychiat. **27:** 1444, 1932.

[36] Goldstein, H.: Muscular dystrophy. Pseudohypertrophic type. Arch. Pediat. **47:** 377, 1930.

[37] Salvioli, G.: Il cuore nella distrofia muscolare progressiva. Clin. pediat. **13:** 51, 1931.

[38] Moschini, S.: Ricerche elettrocardigrafiche in soggetti con distrofia muscolare progressiva. Rev. clin. pediat. **33:** 429, 1935.

[39] Shanks, R. E., Glider, H., Hoagland, C. L.: Studies on diseases of muscle. I. Progressive muscular dystrophy; a clinical review of forty cases. Arch. Neurol. & Psychiat. **52:** 431, 1944.

[40] Johnson, W. J.: Progressive muscular dystrophy. Med. Rec. **144:** 506, 1936.

[41] Yoshida, I.: Über die Myokardveränderung bei der progressiven Muskeldystrophie. Acta Med. Nagasakiensika **2:** 19, 1940.

[42] Mahar, P. J.: Pseudohypertrophic muscular dystrophy in four brothers. Ohio State M. J. **43:** 929, 1947.

[43] Kugel, M. A.: Enlargement of the heart in infants and young children. Am. Heart J. **17:** 602, 1939.

[44] —, and Stoloff, E. G.: Dilatation and hypertrophy of the heart in infants and in young children. With myocardial degeneration and fibrosis (so-called congenital idiopathic hypertrophy). Am. J. Dis. Child. **45:** 828, 1933.

[45] Weisman, S. J.: Congenital idiopathic cardiac hypertrophy. Arch. Path. **33:** 365, 1942.

[46] Mahon, G. S.: Idiopathic hypertrophy of the heart with endocardial fibrosis. Report of two cases. Am. Heart J. **12:** 608, 1936.

Cardiac Actinomycosis

A Case Report and Survey of the Literature

By SAMUEL J. ZOECKLER, M. D.

Involvement of the heart by actinomycetes is rare. A case of actinomycosis, with involvement of the chest wall and clinical pericarditis, with recovery, is reported. The organism, *Actinomyces bovis*, was isolated from the lesion and accurately identified. The literature is reviewed and the modern concepts of pathogenesis and therapy are discussed.

IN 1877 Bollinger described actinomycosis in animals. Wolff and Israel, in 1891, isolated the "Ray Fungus" from a human case. Since then there have been numerous reports of actinomycotic infections in man,[1] and also a few cases of actinomycotic heart disease. However, no case of clinical pericarditis due to *Actinomyces bovis* was found in the available literature. The purpose of this paper is to report such a case and to present some modern concepts of the pathogenesis and treatment of actinomycosis.

CASE REPORT

L. S., a 41 year old white male farmer, was admitted to the hospital June 24, 1950. Two months before admission he noted a pea sized, nontender, nonfluctuant nodule beneath the skin over the right sternal border. This gradually enlarged. Four weeks before entering the hospital he observed that the overlying skin became purplish-blue in color. During this period he had three episodes of severe, stabbing substernal pain. The first, two months prior to admission, lasted 12 hours; the second, one month before admission, lasted 20 minutes; and the third, two days prior to admission, lasted 10 hours. The pain did not radiate but was accentuated by deep inspiration and relieved by assuming the sitting position. All attacks began in the evening while the patient was at rest and were not associated with exertion. Between the acute episodes he noted transient, mild, substernal pain radiating to both shoulders. In the two month period there was a weight loss of 20 pounds.

In 1944 the patient was operated upon for appendicitis. A draining sinus developed at the operative site from which a yellow, serous material exuded with permanent closure after six months.

Physical Examination. The patient was a well developed, well nourished white male of florid complexion, having no obvious distress. Temperature was 100.8 F. Numerous carious teeth were present. A firm subcutaneous mass, measuring 4 by 4 by 2 cm., was found at the level of the seventh rib, extending to the right sternal border. It was attached to skin and deeper structures. The overlying skin had a violaceous hue. The mass was neither tender nor fluctuant. Physical examination of the lungs and abdomen revealed no significant abnormalities. *A loud pericardial friction rub* was heard over the entire precordium and posteriorly at the angle of the left scapula. It was loudest in the left third intercostal space, and was present during voluntary apnea. The heart was not enlarged and a sinus rhythm was present. Blood pressure was 110/70. The normal heart sounds were obscured by the friction rub.

Laboratory Findings. Examination of the blood revealed a white cell count of 8,300 with a normal differential. Red blood count was 4,170,000 with 13.5 Gm. hemoglobin and a hematocrit of 42 per cent. Urinalysis was normal. Typhoid and paratyphoid agglutinations were compatible with previous immunization. An x-ray film of the chest showed prominence of the right hilar markings with some thickening of the pleura on the right above the cardiophrenic angle. There was a soft tissue swelling at the level of the sixth and seventh ribs anteriorly on the right. An electrocardiogram showed slight elevation of the S-T segments in leads I, II and III (fig. 1). Tuberculous pericarditis with involvement of the chest wall was considered. Repeated smears and culture of sputum and gastric content were negative for acid fast bacilli. A skin test with second strength purified protein derivatives was positive.

A Silverman needle biopsy of the mass on the anterior chest wall was obtained on the tenth hospital day and a simple aspiration was performed on the eighteenth hospital day. Both specimens revealed *Actinomyces bovis*. The organism was anaerobic, non-acid fast and gram positive. Its identity was

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confirmed by the laboratories of the United States Public Health Service.

Hospital Course. On the third hospital day the patient was placed on 300,000 units daily of procaine penicillin G in aqueous suspension and received a total of 8,700,000 units. On this regimen the temperature, which had been elevated since admission, became normal on the twelfth hospital day and remained normal throughout his hospital course. The pericardial friction rub was not audible after the sixteenth hospital day. Aureomycin was begun on the thirty-second hospital day, 0.5 Gm. every six hours for a total of 26.0 Gm. On the thirty-third hospital day the lesion on the chest was again aspirated. Smears and culture of the material were

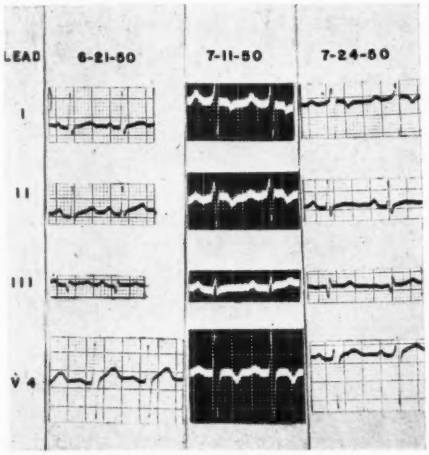

FIG. 1. Electrocardiograms taken at representative periods during the patient's illness demonstrating the changing electrocardiographic picture compatible with pericarditis.

sterile. An electrocardiogram on the sixteenth hospital day showed inverted T waves in leads I, II, aV_L, V_4, V_5 and V_6, and 14 days later continued to show changes compatible with "chronic pericarditis." (fig. 1). The mass slowly resolved and at the time of discharge was present only as an area of slight induration beneath the skin. Two teeth were found to have "apical abscesses." These were removed and cultured but no fungi were recovered. The heart was clinically normal at the time of discharge. Chest x-rays taken on discharge revealed no abnormality in the posteroanterior film. The lateral view demonstrated clearing of the inflammatory process. The patient was discharged on the forty-ninth hospital day. The iodides were not used in treatment.

Examination three months after discharge revealed normal physical findings, a normal electrocardiogram and an unchanged roentgenogram of the chest.

DISCUSSION

It is believed that this represents the first reported case of actinomycosis of the chest wall with associated clinical pericarditis. The organism *Actinomyces bovis* was isolated from samples aspirated from the patient's chest lesion and was accurately identified.

Other cases of actinomycosis involving the heart have been reported.[6, 13, 23, 36–39] Sanford and Voelker in reviewing 670 cases of actinomycosis found no cardiac involvement.[22] Kaspar and Pinner found cardiac involvement in less than 2 per cent of 470 cases.[6] Cornell and Shookhoff[23] in 1944 collected all the cases of actinomycotic involvement of the heart and pericardium and added 3 of their own, bringing the total reported cases to 68. Their study emphasized that actinomycosis usually involves the heart by direct extension. Hematogenous spread is less common. When involvement results from direct extension the pericardium is invaded first, usually with complete obliteration of the pericardial space. The myocardium is commonly involved and not infrequently the process extends to involve and perforate the endocardium. With hematogenous spread the myocardium is the site of primary involvement. Extension to the pericardium or endocardium occurs in only a few such instances.

Sixty of the 68 cases had adequate study. Twenty-three had clinical involvement of the heart or pericardium (see table 2).

Only 4 cases had a pericardial friction rub as the principle manifestations of cardiac disease. All had massive involvement elsewhere and all were fatal. One was due to pyemic involvement and 3 to direct extension.

Certain important clinical facts are brought out by Cornell and Shookhoff in their work: (1) cardiac actinomycosis most commonly results from invasion of the pericardium by direct extension; (2) pyemic involvement of the heart is rare (in such cases the myocardium is first involved); (3) clinical signs of cardiac involvement occur in about 50 per cent of patients with actinomycotic heart disease; and (4) congestive heart failure is the most common clinical manifestation.

Seven additional cases of actinomycotic heart disease were found in the literature.[13, 36–39, 40] In none was the presenting sign a pericarditis. Three cases resembled subacute bacterial endocarditis. Two were fatal and the diagnosis was established at autopsy.[36, 40] The third was apparently cured by massive doses of penicillin. An "actinomyces-like" organism was grown aerobically from several blood samples and was classified as *Actinomyces septicus*.[13] The organisms found in the first 2 cases were identified as *A. graminis* and an "actinomyces" respectively. In 3 cases actinomyces involved the heart by extension from the lungs.[37–39] All were fatal. The cardiac lesion was constrictive pericarditis. The specific etiologic agent (*A. graminis*) was identified in one[37] of these cases. One patient[40] died as a result of hypertensive cardiovascular disease and congestive failure. Necropsy revealed mitral valve lesions from which aerobic actinomyces were cultured.

The case presented here is, therefore, unique in having a pericarditis, without massive involvement elsewhere in the body.

TABLE 1.—*Type of Clinical Involvement in Actinomycotic Heart Disease*

Congestive heart failure	13
Pericardial friction rub	4
Pericardial effusion	2
Circulatory collapse	2
Simulating SBE	1
Cardiac irregularity	1
Total number cases with clinical heart disease	23

TABLE 2.—*The Pathogenic Actinomycetes*

A. *Anaerobic group:*
   Actinomyces bovis (hominis, Wolff-Israel)
B. *Aerobic group:*
   1. Non-acid Fast:
      a. *Actinomyces madurae*
      b. *Actinomyces graminis*
      c. *Actinomyces caprae*
      d. *Actinomyces somaliensis*
   2. Acid Fast: (Also called Nocardia)
      a. *Actinomyces farcinicus*
      b. *Actinomyces asteroides*
      c. *Actinomyces gypsoides*
C. *Facultive aerobic group:*
   Actinomyces muris (*Streptobacillus moniliformis*)

Modern Concepts of Pathogenesis and Treatment

The term actinomycosis includes infections caused by any member of the group of pathogenic fungi known collectively as actinomycetes. The generic name, actinomyces, is applied to all of the forms by Topley and Wilson.[1] However, a small group of the actinomyces, differing from the rest in cultural characteristics, are referred to by other authors as the genus nocardia.[8, 9] A classification of the pathogenic actinomyces, based upon their oxygen requirements, is included in table 2.

The majority of pathogenic actinomyces are anaerobic and take the Gram stain. In the differentiation from the nonpathogenic forms it is important to determine whether the organism is acid fast, aerobic or anaerobic. *Actinomyces bovis*, the causative organism in the majority of human infections, is anaerobic and non-acid fast. *Actinomyces* (*Nocardia*) *asteroides*, a common inhabitant of the human mouth is responsible for about 10 per cent of human infections, chiefly those simulating tuberculosis or involving brain or meninges. It is aerobic and acid fast.[1, 5, 7, 9]

Actinomyces madurae, *A. farcinicus* and *A. muris* (the causative organisms of Madura foot, farcy and ratbite fever respectively) are usually not included under a discussion of human actinomycosis. The other organisms, *A. graminis*, *A. caprae* and *A. somaliensis* have rarely been reported as the causative organisms of human actinomycosis.[1]

The exogenous theory of infection, postulating contact with animals, animal products, grasses or cereals was accepted in the past. Contact with animals suffering from "lumpy jaw," or a habit of chewing on grasses or straws was felt to be important in initiating an actinomycotic infection. More recent investigations point to an endogenous focus, which becomes active under proper conditions of lowered resistance.[12, 20] The following data support this hypothesis:

1. The majority of actinomycetes present on grasses, grains and cereals have proved to be harmless saprophytes. Most common among these is *Actinomyces graminis*.[1, 4, 11, 14]

2. *Actinomyces bovis*, the organism responsi-

ble for the majority of human cases, has been isolated only from the animal body.[1, 4, 11, 14, 21]

3. The human mouth has been established as the normal habitat of *Actinomyces bovis*. It has been isolated from pyorrhea pus, dental scum, salivary calculi, carious teeth and tonsillar crypts.[4, 5, 7, 12, 15, 16]

4. Actinomycotic lesions due to *A. bovis* have been reported following the human bite.[4, 14, 15, 18]

5. Actinomycosis is no more common in rural than urban areas.[4, 7, 19]

6. There is no evidence of man-to-man or animal-to-man transmission except by the human bite.[2, 4, 11, 14, 18]

7. Oral sepsis is frequently associated with the development of actinomycosis, and actinomyces have been cultured from the blood immediately after exodontia.[5, 25]

In the treatment of human actinomycosis the iodides, thymol, irradiation, surgery, sulfonamides, penicillin and aureomycin have been used. At the present time the therapeutic regimen usually consists of the administration of iodides, sulfonamides, penicillin, aureomycin and surgery where indicated.

The use of iodides in human actinomycosis was initiated by Nocard (1885) who found them specific in the treatment of actinomycotic-like lesions in cattle.[4] Since then they have been widely used in treating the human form of the disease. The organism so successfully treated by Nocard and others was *Actinobacillus ligniersi*, for which iodides are specific.[1] It was not an actinomyces. *Actinomyces bovis* has been grown successfully on media containing 2 per cent iodides. At present there seems to be no indication for the use of iodides in human actinomycosis.[4, 5, 26]

Favorable reports have appeared in the literature regarding the use of sulfonamides,[27, 28] penicillin,[3, 5, 7, 11] and surgery,[26, 29] or combinations of the three.[4, 30–32, 34] Reports on the potency of penicillin indicate that some strains of actinomyces are more suspectible than others.[22, 28] The best regimen at present is probably a combination of penicillin and the sulfonamides. Surgical procedures may be necessary to remove pus and dead tissue. The importance of blood transfusions in the debilitated has been stressed by Lyons and others.[30, 34] Aureomycin in the treatment of cervicofacial actinomycosis was recently reported.[19] Apparently aureomycin has little effect on the organism and, until further investigation supports the above work, its use is not recommended.[35]

Summary

1. A case of recovered pericarditis caused by *Actinomyces bovis* is presented.

2. The available literature on cardiac actinomycosis is reviewed and summarized.

3. The pathogenesis and modern therapy of human actinomycosis is discussed.

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References

[1] Wilson, G. S., and Miles, A. A.: Topley and Wilson's Principles of Bacteriology and Immunity. Baltimore, Williams & Wilkins Co., 1946. Vol. II, p. 1269.

[2] Davis, M. I. J.: Analysis of forty-six cases of actinomycosis with special reference to its etiology. Am. J. Surg. **52:** 447, 1941.

[3] Walker, J. M., and Hamilton, J. W.: The treatment of actinomycosis with penicillin. Ann. Surg. **121:** 373, 1945.

[4] Hollis, W. J., and Hargrove, M. D.: Actinomycosis: a report of twelve cases with special reference to a mediastinal case. New Orleans M. & S. J. **99:** 499, 1947.

[5] Kolouch, F., and Peltier, L. F.: Actinomycosis. Surgery **20:** 401, 1946.

[6] Kasper, J. A., and Pinner, M.: Actinomycosis of the heart. Arch. Path. **10:** 687, 1930.

[7] Sanford, G. E., and Barnes, R. O.: Massive penicillin therapy of abdominal actinomycosis. Surgery **25:** 711, 1949.

[8] Dubos, R. J: Bacterial and Mycotic Infections of Man. Philadelphia, J. B. Lippincott Co., 1948. P. 578.

[9] Waksman, S. A., and Henrici, A. T.: The nomenclature and classification of the actinomycetes. J. Bact. **46:** 337, 1943.

[10] Harris, A. M., and Priestley, J. B.: Actinomycosis: report of a case with miliary chest lesions. J. Lab. & Clin. Med. **29:** 815, 1944.

[11] Keeney, E. L.: Medical mycology. M. Clin. North America **29:** 323, 1945.

[12] Rosebury, T., Epps, L. J., and Clark, A. R.: Study of isolation, cultivation and pathogenicity

of Actinomyces israeli recovered from human mouth and actinomycosis in man. J. Infect. Dis. **74:** 131, 1944.

[13] MacNeal, W. J., Blevins, A., and Duryee, A. W.: Clinical arrest of endocardial actinomycosis after 44 million units of penicillin. Am. Heart J. **31:** 668, 1946.

[14] Cope, Z.: Actinomycosis. New York, Oxford University Press, 1938.

[15] Musser, J. H.: Internal Medicine. Philadelphia, Lea & Febiger, 1945. P. 433.

[16] Weller, C. V.: Incidence and pathogenesis of tonsillar concretions. Ann. Otol., Rhinol., & Laryngol. **33:** 79, 1924.

[17] Wilkinson, H. F.: Pathologic changes in tonsils. Arch. Otolaryng. **10:** 127, 1929.

[18] Robinson, R. A.: Actinomycosis of subcutaneous tissue of the forearm secondary to a human bite. J. A. M. A. **124:** 1049, 1944.

[19] McVay, L. V., Jr., Dunavant, D., Guthrie, F., and Sprunt, D. H.: Treatment of actinomycosis with aureomycin. J. A. M. A. **143:** 1067, 1950.

[20] Lord, F. T.: A contribution to the etiology of actinomycosis: the experimental production of actinomycosis in guinea pigs. Boston M. & S. J. **163:** 82, 1910.

[21] Boyd, W.: A Textbook of Pathology, ed. 4. Philadelphia, Lea & Febiger, 1943. Pp. 185–186.

[22] Sanford, A. H., and Voelker, M.: Actinomycosis in the United States. Arch. Surg. **11:** 809, 1925.

[23] Cornell, A., and Shookhoff, H. B.: Actinomycosis of the heart simulating rheumatic fever. Arch. Int. Med. **74:** 11, 1944.

[24] White, P. D.: Heart Disease. New York, Macmillan Co., 1944. P. 402.

[25] Northrop, P. M., and Crowley, M. C.: The prophylactic use of sulfathiazole in transient bacteremia following the extraction of teeth. J. Oral Surg. **1:** 19, 1943.

[26] Wangensteen, O. H.: Actinomycosis of the thorax with report of a case successfully operated upon. J. Thoracic Surg. **1:** 612, 1932.

[27] Pillsbury, N. R., and Wassersug, J. D.: Pulmonary actinomycosis treated with sulfonamides. New England J. Med. **230:** 72, 1944.

[28] Dobson, L., and Cutting, W. C.: Penicillin and sulfonamides in the treatment of actinomycosis. J. A. M. A. **128:** 856, 1945.

[29] Wangensteen, O. H.: The role of surgery in the treatment of actinomycosis. Ann. Surg. **104:** 752, 1936.

[30] Gage, M., Lyons, C., and DeCamp, P. T.: Essential therapeutic adjuvants in surgical arrest of Wolff-Israel actinomycosis. Ann. Surg. **126:** 568, 1947.

[31] McCrea, J. H., Steven, R. A., and Williams, O. O.: Actinomycotic infection of soft tissues of the neck. J. Lab. & Clin. Med. **30:** 509, 1945.

[32] Hendrickson, G. G., and Lehman, E. P.: Cervicofacial actinomycosis successfully treated by penicillin without surgical drainage. J. A. M. A. **128:** 438, 1945.

[33] Uhr, N.: Bacterial endocarditis: report of a case in which the causative organism was actinomyces bovis. Arch. Int. Med. **64:** 84, 1939.

[34] Lyons, C., Owen, C. R., and Ayers, W. B.: Sulfonamide therapy in actinomycotic infection. Surgery **14:** 99, 1943.

[35] Rutledge, W.: Personal Communication, Lederle Laboratories, (July) 1950.

[36] Beamer, P. R., Reinhard, E. H., and Godoff, I. I.: Vegetative endocarditis caused by higher fungi and bacteria. Am. Heart J. **29:** 99, 1945.

[37] Lynch, J. P., and Holt, R. A.: Pulmonary actinomycosis due to Actinomyces graminis. Ann. Int. Med. **23:** 91, 1945.

[38] Gose, A. C.: A case of constrictive pericarditis due to actinomycosis. Memphis M. J. **17:** 56, 1942.

[39] Lidbeck, W.: Actinomycosis. West. J. Surg. **50:** 498, 1942, Case II.

[40] Wedding, E. S.: Actinomycotic endocarditis. Arch. Int. Med. **79:** 203, 1947.

The Effect of "Salt" Hypertension on Atherosclerosis in Chicks Fed Mash without a Cholesterol Supplement

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With the technical assistance of P. Johnson

Hypertension induced by adding sodium chloride to the diet (0.9 per cent) or drinking water (8 per cent) of chicks on plain mash did not intensify spontaneous atherosclerosis or lead to atherosclerotic lesions of the induced type.

HYPERTENSION in man is typically associated with increased incidence and severity of atherosclerosis. Conversely, many people with atherosclerosis have hypertension.[1-13] However, longstanding hypertension may be unaccompanied by atherosclerosis, and atherosclerosis may develop in normotensive persons.

Despite numerous clinical studies analyzing and correlating these facts, the precise interrelationships between the two conditions, hypertension and atherosclerosis, remain obscure. This lack of clarity stems first of all from the inadequacy of our understanding concerning the pathogenesis of both hypertension and atherosclerosis. It is aggravated by the paucity of experimental investigations of the interrelationships between the two states. The meager laboratory data stand in marked contrast to the massive clinical findings. In view of this situation, we undertook to ascertain the effects of various forms of experimental hypertension on different types of experimental atherosclerosis. The present report presents our findings in one project of this series: a study of the effect of "salt" hypertension on atherosclerosis in the chick.[14, 15]

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METHODS

Seventy-two 1 day old Hy-line cockerels were obtained from a certified hatchery and reared in a battery brooder. Upon receipt in the laboratory, these chicks were divided into three groups of 24 birds each. As indicated by the experimental regimens (table 1), substitution of 0.9 per cent saline solution for drinking water (group 1) and addition of up to 8 per cent salt to the mash (group 2) were used to induce hypertension.[16-20] The effect of this hypertension upon atherogenesis was assayed by comparison with a control group of chicks (group 3).

Chicks were weighed weekly throughout the experiment. Blood pressures were determined serially after 8, 12, 17, 25 and 35 weeks on the experimental regimens. They were recorded in unanesthetized, quiescent chicks by direct puncture of a sciatic artery. At 8, 12, and 35 weeks, systolic and diastolic pressures were optically recorded with a Hamilton manometer.[21] At 17 and 25 weeks, mean blood pressures were read off a mercury manometer.

Comb size indexes were obtained periodically, using established methods for this measurement.[22, *] After 35 weeks of experimental feeding, birds from each group were killed by decapitation and exsanguination. At sacrifice, plasmas from individual chicks were collected and analyzed for total cholesterol by the method of Schoenheimer and Sperry.[23] At autopsy, all the viscera were examined and the gross findings recorded. The hearts and great vessels were carefully inspected for evidence of gross atheromatous plaques. Specimens from chicks of the three groups were mixed indiscriminately and examined consecutively as unknowns. Lesions, if any, were recorded graphically on special forms and graded grossly 0 to 4 according to criteria previously described.[24] Formalin-fixed sections were prepared and stained with hematoxylin-eosin or Sudan IV.

* Comb size index (P) in units = comb length (cm.) × comb height (cm.)

Results

Blood Pressures. The average of the blood pressures for the control (group 3) Hy-line cockerels (163/138 mm. Hg) was somewhat higher than that previously recorded in Leghorns in this laboratory (132/117 mm. Hg).[16, 25] A majority of birds in both groups receiving salt (groups 1 and 2) exhibited significant elevations of blood pressure by the eighth week after institution of the experimental regimens. Subsequently most of these chicks continued to exhibit these pressure increments. Hence the salt-induced hypertension was of a sustained character. The mean blood pressures of the three groups at the end of the experiment are presented with statistical analysis[26] in table 2. These data include pressures of all chicks still alive in these groups at the end of the experiment (cf. table 3). Further analysis reveals that in groups 1 and 2, 62 and 38 per cent, respectively, of the chicks had terminal pressures greater than 180/150 mm. Hg; in contrast, only one bird in the control group had a blood pressure elevation of this order (chick #409, group 3, table 3).

Table 1.—*Experimental Regimens**

	Feed	Fluid
Group 1 (Saline)	Plain mash†	0.9% NaCl
Group 2 (salt)	Plain mash & salt‡	Tap water
Group 3 (Control)	Plain mash	Tap water

* Food and water were given *ad libitum* throughout.

† Commercial chick starter mash of known composition.[27]

‡ Over the first 12 experimental weeks, the salt supplement mixed in with the mash was increased stepwise from 1 to 8 per cent.

Findings in Aorta. The gross gradings for aorta atherosclerosis are presented in detail in table 3 and summarized in table 4. The morphology of the aorta lesions in all groups was typical of chick spontaneous atherosclerosis.[14, 15, 27] Lesions were confined to the abdominal aorta. No thoracic aorta lesion of the cholesterol-induced type was observed in either hypertensive or normotensive birds. Over-all comparison of the three groups reveals no significant differences in incidence and severity of atherosclerosis (table 4*A*—all birds). Further analysis, comparing only the hypertensive birds of experimental groups 1 and 2 with the normotensive controls (table 4*B*), reveals a higher incidence of spontaneous aorta atherosclerosis in the hypertensive chicks, particularly in the birds receiving saline (group 1). In view of the size of groups and the known range of variability in the incidence of spontaneous atherosclerosis in control chicks,[27] these differences (54 and 40 per cent incidence vs. 22 per cent—table 4*B*) are of questionable significance. This interpretation is supported by the data on severity of atherosclerosis, which demonstrate no significant, consistent differences in mean grading or incidence of more severe lesions in the hypertensive chicks vs. the normotensive controls. Microscopic sections of random blocks of cardiac tissue revealed no evidence of coronary atherosclerosis in the chicks with "salt" hypertension.

Miscellaneous Findings. All three groups of animals ate well throughout the experiment.

Table 2.—*Terminal Blood Pressures (in mm. Hg)*

	Mean		Range		S.D.*		S.E.†	
	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
Group 1 (Saline)	183	150	151–212	126–169	14.1	10.4	3.1	2.3
Group 2 (Salt)	181	148	155–215	127–182	17.0	14.5	4.7	4.0
Group 3 (Control)	163	138	144–193	108–163	16.6	14.4	5.2	4.6

* S.D. = standard deviation of the mean, calculated from the formula, $S.D. = \sqrt{\frac{\Sigma(x_i - \bar{x})^2}{N-1}}$

† S.E. = standard error of the mean, calculated from the formula, $S.E. = \frac{S.D.}{\sqrt{N}}$[26]

TABLE 3.—*Blood Pressures and Gross Gradings for Aorta Atherosclerosis of Individual Chicks after Thirty-five Weeks of Experimental Feeding*

Group 1 (Saline)					Group 2 (Salt)					Group 3 (Control)				
No.*	Thor.	Abd.	Sum	B.P.	No.	Thor.	Abd.	Sum	B.P.	No.	Thor.	Abd.	Sum	B.P.
358	0	1½	1½	175/145	417	0	0	0	198/147	407	0	0	0	144/121
164	0	0	0	208/168	248	0	0	0	180/150	693	0	0	0	147/131
317	0	½	½	203/160	323	0	0	0	197/157	315	0	0	0	163/135
352	0	1	1	187/159	240	0	0	0	167/127	409	0	0	0	193/163
353	0	0	0	189/151	669	0	0	0	178/148	351	0	0	0	178/147
301	0	½	½	180/153	373	0	0	0	155/139	408	0	1	1	175/147
360	0	0	0	212/169	443	0	0	0	178/136	416	0	0	0	149/125
309	0	0	0	173/138	247	0	½	½	—/182	368	0	0	0	170/143
460	0	2¼	2¼	182/154	84	0	½	½	—/169	406	0	1	1	167/140
392	0	0	0	175/153	311	0	0	0	—/143	470	0	0	0	145/108
348	0	0	0	167/138	294	0	0	0	172/148	674	0	0	0	—
253	0	0	0	151/126	328	0	0	0	163/137					
457	0	0	0	173/143	357	0	½	½	178/145	692	0	0	0	—
46	0	1	1	197/155	339	0	0	0	—	159	0	0	0	—
312	0	1	1	176/153	330	0	0	0	—	585	0	0	0	—
375	0	0	0	185/154						742	0	¼	¼	—
355	0	1	1	182/148						699	0	¼	¼	—
459	0	0	0	—						555	0	0	0	—
396	0	0	0	170/135						492	0	2¼	2¼	—
347	0	0	0	187/156						493	0	1	1	—
302	0	0	0	183/153						491	0	0	0	—
668	0	2	2	186/149						496	0	1¼	1¼	—

* No. is chick's number.
Thor. is thoracic aorta.
Abd. is abdominal aorta.
B.P. is blood pressure in mm. Hg.

TABLE 4.—*Summary of Data on Terminal Blood Pressures and Gross Gradings for Aorta Atherosclerosis*

	Mean B.P.*	No. of birds	No. with lesions	Per cent with lesions	Gradings†			No. with lesions 1 or >	Per cent with lesions 1 or >
					Thor.	Abd.	Sum		
A. All Birds									
Group 1 (Saline)	183/150	22	8	36	0	1¼	1¼	7	32
Group 2 (Salt)	181/148	15	3	20	0		½	0	0
Group 3 (Control)	163/138	21	7	33	0	1	1	4	19
B. Birds of Groups 1 and 2 with B.P. > 180/150§									
Group 1 (Saline)	191/156	13	7	54	0	1¼	1¼	5	38
Group 2 (Salt)	199/161	5	2	40	0	½	½	0	0
Group 3 (Control)‡	159/135†	9	2	22	0	1	1	2	22
C. Birds of Groups 1 and 2 with B.P. < 180/150§									
Group 1 (Saline)	170/141	8	2	25	0	1¼	1¼	2	25
Group 2 (Salt)	170/140	8	1	13	0	½	½	0	0
Group 3 (Control)‡	159/135†	9	2	22	0	1	1	2	22

* Symbols same as in table 3.
† Exclusive of bird No. 409, with a terminal pressure of 193/163 mm. Hg; this chick was free of aorta lesions.
‡ Figure represents mean grading for atherosclerosis in birds with lesions; it is not a mean grading for the whole group.
§ See text.

The three groups had practically identical plasma total cholesterol levels (means and ranges) at the end of the study. These were in accord with established norms for this value.[27] Apparently the experimental regimens had no effect on plasma total cholesterol concentration. Data on water intake, weight gain, and excretory pattern in the experimental groups were essentially in accord with previous reports on similarly treated chicks, as were also the remaining necropsy findings.[16, 19] Comb size indexes were consistently and significantly lower in the two experimental groups, compared with the controls. Thus the comb size indexes (P in units) at the end of study were: group 1, 78; group 2, 78; group 3 (control), 107. This finding is suggestive of decreased androgenic activity in the experimental chicks.[22]

Discussion

"Salt" hypertension has little or no gross effect on atherogenesis in chicks fed mash without a cholesterol supplement. No significant increase in incidence or severity of spontaneous lesions of the abdominal aorta supervenes. No lesions of the thoracic aorta of the cholesterol-induced variety develop.

Desoxycorticosterone-induced (DCA) hypertension likewise has only a slight effect on spontaneous atherogenesis in cockerels fed plain mash, and also fails to bring about the development of lesions of the cholesterol-induced type.[27, *] Further, in rabbits, dogs, sheep and goats hypertension *alone* does not induce atherosclerosis.[6, 27-34] In all these experiments, animals subsisted on diets devoid of any cholesterol supplement; they were apparently normocholesterolemic throughout.

In contrast to these negative results, hypertension does significantly influence atherogenesis in cholesterol-fed animals. Desoxycorticosterone-induced hypertension intensifies atherogenesis of the cholesterol-induced type in chicks fed 0.25 per cent cholesterol mash.[27] In cholesterolized rabbits, hypertension† similarly increases the incidence and severity of cholesterol-induced atherosclerosis.[30, 35-37] Animals in these experiments are slightly to severely hypercholesterolemic.

These studies call to mind Aschoff's statement: "From plasma of low cholesterol content no deposition of lipids will occur even though the mechanical conditions are favorable."[3] They suggest that hypertension, per se, is not a cause of atherosclerosis. Rather it acts only in an auxiliary way to accelerate and aggravate atherogenesis induced by other factors, particularly alterations in lipid metabolism.[5, 10, 27, 30, 39]

Summary

1. "Salt" hypertension has little or no effect on spontaneous atherogenesis in the abdominal aorta of chicks fed mash without a cholesterol supplement.

2. In such birds "salt" hypertension does not lead to the development of gross lesions in the thoracic aorta of the cholesterol-induced type.

Acknowledgment

We wish to express our appreciation to the other members of the department's arteriosclerosis project research team, Miss Christine Bolene, Deborah V. Dauber research assistant; Dr. Ruth Pick, histopathologist; Miss Marilyn Dudley, chemist; Mr. Grady Crowley, laboratory technician. Without their skilled cooperation this study could not have been consummated.

REFERENCES

[1] Fishberg, A. M.: Hypertension and Nephritis, ed. 4. Philadelphia, Lea & Febiger, 1939.

[2] Lange, F.: Hypertension in relation to arteriosclerosis. In Cowdry, E. V.: Arteriosclerosis. New York, Macmillan, 1933.

[3] Daley, R. M., Ungerleider, H. E., and Gubner, R. S.: Prognosis in hypertension. J. A. M. A. **121:** 383, 1943.

[4] Yater, W. M., Traum, A. H., Brown, W. G., Fitzgerald, R. P., Geisler, M. A., and Wilcox, B. B.: Coronary artery disease in men eighteen to thirty-nine years of age. Am. Heart J. **36:** 334, 481, 683, 1948.

* Both "salt" and desoxycorticosterone-induced hypertensions in these experiments were only moderate in degree. It remains to be demonstrated whether hypertension of greater severity influences atherogenesis in chicks fed diets devoid of cholesterol supplement.

† Various forms of hypertension were utilized, including compression of the abdominal aorta above the renal arteries,[30, 35, 36] and maintenance of animals in an upright position (orthostatic hypertension).[37]

[5] ROSENTHAL, S. R.: Studies in atherosclerosis: chemical, experimental and morphologic. Arch. Path. **18:** 473, 660, 1934.

[6] HUEPER, W. C.: Arteriosclerosis. Arch. Path. **38:** 162, 245, 350, 1944; **39:** 51, 117, 187, 1945.

[7] SMITH, T. M.: Coronary arteriosclerosis in the Negro. J. Nat. M. A. **38:** 193, 1946.

[8] WHITE, N. K., EDWARDS, J. E., AND DRY, T. J.: The relationship of the degree of coronary atherosclerosis with age, in men. Circulation **1:** 645, 1950.

[9] ACKERMAN, R. F., DRY, T. J., AND EDWARDS, J. E.: Relationship of various factors to the degree of coronary atherosclerosis in women. Circulation **1:** 1345, 1950.

[10] GUBNER, R., AND UNGERLEIDER, H. E.: Arteriosclerosis. Am. J. Med. **6:** 60, 1949.

[11] DOCK, W.: The causes of arteriosclerosis. Bull. New York Acad. Med. **26:** 182, 1950.

[12] CLAWSON, B. J.: Coronary sclerosis. Am. Heart J. **17:** 387, 1939.

[13] ——: Incidence of types of heart disease among 30,265 autopsies, with special reference to age and sex. Am. Heart J. **22:** 607, 1941.

[14] KATZ, L. N., AND DAUBER, D. V.: The pathogenesis of atherosclerosis. J. Mt. Sinai Hosp. **12:** 382, 1945.

[15] ——, STAMLER, J., AND HORLICK, L.: Cholesterol metabolism in health and disease: its relationship to arteriosclerosis.Am. Pract. **1:** 461, 1950.

[16] LENEL, R., KATZ, L. N., AND RODBARD, S.: Arterial hypertension in the chicken. Am. J. Physiol. **152:** 557, 1948.

[17] SELYE, H.: Production of nephrosclerosis by overdosage with desoxycorticosterone acetate. Canad. M. A. J. **47:** 515, 1942.

[18] ——, AND STONE, H.: Role of sodium chloride in production of nephrosclerosis by steroids. Proc. Soc. Exper. Biol. & Med. **52:** 190, 1943.

[19] KRAKOWER, C. A., AND HEINO, H. E.: Relationship of growth and nutrition to cardiorenal changes induced in birds by a high salt intake. Arch. Path. **44:** 143, 1947.

[20] SAPIRSTEIN, L. A., BRANDT, W. L., AND DRURY, D. R.: Production of hypertension in the rat by substituting hypertonic sodium chloride solutions for drinking water. Proc. Soc. Exper. Biol. & Med. **73:** 82, 1950.

[21] KATZ, L. N., FRIEDMAN, M., RODBARD, S., AND WEINSTEIN, W.: Observations on the genesis of renal hypertension. Am. Heart J. **17:** 334, 1939.

[22] PARKS, A. S., AND EMMENS, C. W.: Effect of androgens and estrogens on birds. Vitamins & Hormones **2:** 361, 1944.

[23] SCHOENHEIMER, R., AND SPERRY, W. M.: A micromethod for the determination of free and combined cholesterol. J. Biol. Chem. **106:** 745, 1934.

[24] HORLICK, L., AND KATZ, L. N.: The relationship of atheromatosis development in the chicken to the amount of cholesterol added to the diet. Am. Heart J. **38:** 336, 1949.

[25] RODBARD, S., AND TOLPIN, M.: A relationship between the body temperature and the blood pressure in the chicken. Am. J. Physiol. **151:** 509, 1947.

[26] FISHER, R. A.: Statistical Methods for Research Workers, ed. 10. London, Oliver & Boyd, 1948.

[27] KATZ, L. N., AND STAMLER, J.: Experimental Atherosclerosis. Springfield, Ill., Charles C Thomas. In press.

[28] RÜHL, A., cited by ROSENTHAL, S. R.: Studies in atherosclerosis: chemical, experimental and morphologic. Arch. Path. **18:** 473, 660, 1934.

[29] NUZUM, F. R., SEEGAL, B., GARLAND, R., AND OSBORNE, M.: Arteriosclerosis and increased blood pressure. Arch. Int. Med. **37:** 733, 1926.

[30] ANITSCHKOW, N.: Experimental arteriosclerosis in animals. In COWDRY, E. V.: Arteriosclerosis. New York, Macmillan, 1933.

[31] STAMLER, J., KATZ, L. N., AND RODBARD, S.: Serial renal clearances in dogs with nephrogenic and spontaneous hypertension. J. Exper. Med. **90:** 511, 1949.

[32] GOLDBLATT, H., KAHN, J. R., AND LEWIS, H. A.: Studies on experimental hypertension. XIX. The production of persistent hypertension in sheep and goats. J. Exper. Med. **77:** 297, 1943.

[33] ——: The renal origin of hypertension. Physiol. Rev. **27:** 120, 1947.

[34] BRAUN-MENENDEZ, E., FASCIOLO, J. C., LELOIR, L. F., MUNOZ, J. M., AND TAQUINI, A. C. (translated by DEXTER, L.): Renal Hypertension. Springfield, Charles C Thomas, 1946.

[35] ANITSCHKOW, N.: Atherosklerose der Aorta und deren Entstehungsbedingungen. Beitr. z. path. Anat. u. z. allg. Path. **56:** 379, 1914.

[36] DILL, L. V., AND ISENHOUR, C. E.: Occurrence of atheroma in the aorta in rabbits with renal hypertension. Arch. Path. **33:** 655, 1942.

[37] WILENS, S. L.: The effect of postural hypertension on the development of atheromatosis in rabbits fed cholesterol. Am. J. Path. **19:** 293, 1943.

[38] ASCHOFF, L.: Lectures in Pathology. New York, Paul B. Hoeber, 1924.

[39] FABER, M.: The cholesterol content of the human aorta in relation to the serum cholesterol concentration. Acta med. Scandinav. **125:** 418, 1946.

Plasma Cholesterol Levels during Rapid Weight Reduction

By WELDON J. WALKER, LIEUTENANT COLONEL, M. C., U. S. A., AND JAMES A. WIER, LIEUTENANT COLONEL, M. C., U. S. A.

Twenty-seven obese individuals underwent rapid weight reduction by rigid caloric restriction. During this time there was a slight over-all drop in plasma cholesterol levels. Patients undergoing most rapid weight loss showed the greatest drop in plasma cholesterol. Fear of elevating the plasma cholesterol need not deter the physician from subjecting obese patients to rapid weight reduction

MANY writers,[1–3] have pointed out the serious danger to life of obesity. In spite of general agreement that weight reduction is urgently indicated in overweight individuals there is considerable difference of opinion as to how rapidly it should be accomplished. It has been our experience that rapid weight loss is no more unpleasant for the patient than gradual reduction and is much more likely to succeed, since the tangible results encourage the patient to continue until his desired goal is achieved. Dilatory weight reduction often fails because results are so slowly realized that the patient becomes discouraged and stops after a few weeks trial. Newburgh[1] has advocated rapid weight reduction and reported the case of an unusually obese male who sustained the amazing loss of 286 pounds in a year's time with marked improvement in health. Because of apparent correlation between elevation of plasma cholesterol and the incidence of arteriosclerosis considerable interest has been directed toward learning the effects of nutritional variables on cholesterol levels. Shope[4] has reported an early rise in the level of serum cholesterol in both man and experimental animals during fasting, and the concept of "starvation hyperlipemia" has been accepted by some as an established fact. However, many workers have been unable to demonstrate elevation in plasma cholesterol during fasting or starvation in man or experimental animals.[5–8] Reports are variable and conflicting. Harrison[9] seemed to have accepted the concept of starvation hyperlipemia when he stated, "It should be remembered that weight reduction causes the patient to utilize large amounts of his own fat, and hence is equivalent to a high fat diet . . . Hence, weight reduction should usually be carried out slowly rather than rapidly." The present study was undertaken for the purpose of determining whether high plasma cholesterol levels resulted during the early stages of rapid weight reduction.

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STUDY

The 27 overweight patients included in the study were placed on reducing diets after their weights had been recorded and a fasting plasma cholesterol had been obtained. Reducing diets of 600 or 800 calories daily were used in most cases. The individuals studied had been hospitalized for medical or surgical conditions not directly related to their corpulent state. Total plasma cholesterol determinations were made at intervals during the early stages of weight reduction. Patients with diabetes were excluded from the study since the state of diabetic control would be expected to influence cholesterol levels. Patients showing evidence of congestive heart failure were excluded since their weight fluctuations would not necessarily reflect loss of body tissue. Those who failed to show an average weight loss of at least 2 pounds per week during the period of observation were excluded since there was doubt that they had adhered to the prescribed diet. The majority of patients lost 4 or more pounds per week. Observations did not extend beyond four weeks and very few beyond three weeks since it has been previously reported that if weight reduction is carried to malnutrition or semistarvation the cholesterol level falls with the state of nutrition.[7, 8]

RESULTS AND DISCUSSION

Forty plasma cholesterol determinations were made during the period of rapid weight reduction; twenty-seven were lower and thirteen higher than earlier control levels. There seemed to be no significant increase or decrease

TABLE 1.—*Tabulation of Plasma Cholesterol Determinations during Weight Reduction*

	Control	1st Week	2nd Week	3rd Week	4th Week
Case 1, Chol.	209	187			
Wt.	241	234			
Case 2, Chol.	239		242		
Wt.	160		154		
Case 3, Chol.	373			290	
Wt.	152			142	
Case 4, Chol.	150		177		
Wt.	176		164		
Case 5, Chol.	265		257		
Wt.	221		212		
Case 6, Chol.	254		270		
Wt.	200		191.5		
Case 7, Chol.	278	215		233	
Wt.	195	190		180	
Case 8, Chol.	179	239	186		
Wt.	172	166	165		
Case 9, Chol.	203			152	
Wt.	206.5			201	
Case 10, Chol.	186	264	290		
Wt.	145	141.5	140		
Case 11, Chol.	264	230			
Wt.	190.75	187			
Case 12, Chol.	337	326			
Wt.	227	219			
Case 13, Chol.	245		230	249	
Wt.	167		160	157	
Case 14, Chol.	223	251	217		
Wt.	217	213	208		
Case 15, Chol.	220			207	
Wt.	196			189	
Case 16, Chol.	293	281			
Wt.	172	168			
Case 17, Chol.	232		211		
Wt.	189.25		184.5		
Case 18, Chol.	222	205		175	
Wt.	200	197		188	
Case 19, Chol.	303	285	275	287	
Wt.	194	190	185.5	183.5	
Case 20, Chol.	319	266			
Wt.	195.5	192.5			
Case 21, Chol.	259		261		
Wt.	176		172		
Case 22, Chol.	424			400	401
Wt.	160			153	149
Case 23, Chol.	233	266		224	
Wt.	222.5	215		215	
Case 24, Chol.	284	277			
Wt.	109	204			
Case 25, Chol.	223		218	266	246
Wt.	180		176	170	166
Case 26, Chol.	244			174	
Wt.	217			206.5	
Case 27, Chol.	322			242	281
Wt.	130			125	122

Cholesterol values are in mg. per 100 cc.; weight of patients is in pounds.

in cholesterol levels during the first two weeks of weight reduction. The average of determinations taken during the first week of weight reduction was 2.9 mg. per 100 cc. lower than values for these same patients taken before weight reduction started. Determinations taken during the second week of weight reduction averaged 6.3 mg. per 100 cc. higher than control levels. These variations are well within the range of normal fluctuation or laboratory error. However, determinations taken during the third week averaged 32.5 mg. per 100 cc. lower than control values. It is of particular interest that average values for the 12 patients who lost from 2 to 4 pounds per week dropped 4.4 mg. per 100 cc. while the 15 patients who lost 4 or more pounds per week showed a greater average drop—14.7 mg. per 100 cc. These latter cases might have been expected to show "starvation hyperlipemia." Poindexter[10] followed the plasma cholesterol levels in 30 patients during slow weight reduction; his results showed quite wide and variable fluctuations both above and below the control levels. He attributed those showing increased cholesterol levels to the "starvation" effect even though these patients had an average weight loss of less than 1 pound

TABLE 2.—*Variation in Cholesterol Values during Weight Reduction*

	1st Week	2nd Week	3rd Week
Determinations Showing Increased Cholesterol Levels	4	6	2
Determinations Showing Decreased Cholesterol Levels	9	6	10
Average Change of Cholesterol Value mg. per 100 cc.	−2.9	+6.3	−32.5

TABLE 3.—*Variation of Cholesterol Values in Relation to Rate of Weight Loss*

	Less than 4 lbs./week	Greater than 4 lbs./week
Determinations Showing Increased Cholesterol Levels	7	6
Determinations Showing Decreased Cholesterol Levels	12	15
Average Change of Cholesterol Value*	−4.4	−14.7

* Mg. per 100 cc.

per week. Our patients showed similar fluctuations in plasma cholesterol levels during a much more rapid weight reduction but if there was any trend it seemed toward lower not higher levels.

Many fears concerning rapid weight reduction have been based on the concept that fat stores of the body are relatively stable and weight reduction would necessarily cause increased fat mobilization with consequent elevation of blood cholesterol since it is one of the chief vehicles for fat transport. However, recent studies indicate that fat depots are normally in a constant state of dynamic flux with a daily turnover many times in excess of the amount that would be burned during a period of starvation.[11]

The diet offered our patients was extremely low in fat and relatively high in protein and bulk. No effort was made to restrict cholesterol intake; in fact, most patients received one egg daily. Calculated daily intakes on the 800 calorie diet were: carbohydrate 94 Gm., protein 82 Gm., fat 11 Gm., cholesterol 0.62 Gm.

Conclusion

Patients undergoing rapid weight reduction as a result of rigid caloric restriction did not manifest an over-all elevation in total plasma cholesterol. The fear of elevating the plasma cholesterol need not deter the physician from subjecting obese patients to rapid weight reduction.

REFERENCES

[1] Newburgh, L. H.: Obesity. Arch. Int. Med. **70**: 1033, 1942.

[2] Gastineau, C. F., and Rynearson, E. H.: Obesity. Ann. Int. Med. **27:** 883, 1947.

[3] Walker, W. J.: Obesity as a problem in preventive medicine. Armed Forces M. J. **1:** 393, 1950.

[4] Shope, R. E.: Sugar and cholesterol in the blood serum as related to fasting. J. Biol. Chem. **75**: 101, 1927.

[5] Lennox, W. G., O'Connor, M., and Bellinger, M.: Chemical changes in the blood during fasting in the human subject. Arch. Int. Med. **38**: 553, 1926.

[6] Entenman, C., Changus, G. W., Gibbs, G. E., Charkoff, I. L.: The response of lipid metabolism to alterations in nutritional state. J. Biol. Chem. **134:** 59, 1940.

[7] Man, E. B., and Gildea, E. F.: Serum lipoids in malnutrition. J. Clin. Investigation **15:** 203, 1936.

[8] Brozek, J., Wells, S., and Keys, A.: Medical aspects of semistarvation in Leningrad. Am. Rev. Soviet Med. **4:** 70, 1946.

[9] Harrison, T. R.: Editorial comment in Yearbook of General Medicine. Chicago, Yearbook Publishers, 1948. Page 514.

[10] Poindexter, C. A., and Bruger, M.: Effect of low caloric diets and resultant loss in weight on plasma cholesterol in the obese. Arch. Int. Med. **56:** 884, 1935.

[11] Schoenheimer, R.: The Dynamic State of Body Constituents. Cambridge, Harvard University Press, 1942. P. 22.

The Age Factor in Hypercholesteremia and Atheromatosis in the Chick

By S. Rodbard, Ph.D., L. N. Katz, M.D., C. Bolene, B.A., R. Pick, M.D., M. Lowenthal, M.D., and G. Gros, M.D.

The development of atherosclerosis in very young chicks challenges the concept that atherogenesis depends upon senescence. Instead, the age period, rather than age, seems to be the more significant factor in atherogenesis. This is so since the regulation of the plasma cholesterol level is shown to vary at different age periods. During the first two months of life of the chick, a resistance to hypercholesteremia and atheromatosis is seen. At the eighth week, corresponding to the time of puberty, the plasma cholesterol rises markedly, despite an unchanged dietary regimen. The resistance to vascular lesions disappears and atheromatosis develops rapidly over the next few weeks. This indicates that endogenous mechanisms dependent upon the age period are important factors in the tendency to hypercholesteremia and atherogenesis.

IN AN attempt to define the respective roles of age and aging in the susceptibility to hypercholesteremia and atheromatosis, we have recently studied the effect of a high cholesterol diet in the newly hatched chick. The very young chick was used because it was hoped in this way to eliminate as much as possible the effects of the aging process and of injuries to vessel walls which may occur in the course of the life of the animal.

Progressive formation of fibrous connective tissue and modifications of the ground substance of the arterial tree occur with increasing age. These facts have led to the concept that arteriosclerosis is a normal aging process superimposed on these basic changes.[1] With aging of an animal, the arteries are exposed to successive noxious stimuli with consequent additive injury. The production of atheromatosis in very young animals therefore would give evidence concerning the necessity of vascular injury or senile metamorphosis of the vascular tissues as a precondition for the atherosclerotic process.

For these reasons we have attempted to produce atheromatosis by supplementing the diet of newly hatched chicks with cholesterol. In the course of the study, it was found that the age factor played an entirely unexpected role in the regulation of hypercholesterolemia and atherogenesis. A seasonal effect was also noted.

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Methods

A total of 381 Hyline cockerels, one day old, were bought from a local distributor on two separate occasions. The first series of 166 chicks arrived in the laboratory Aug. 1, 1949, and was placed immediately on experimental diets. The animals were divided into a control group of 73 chicks which received normal starter mash and an experimental group of 93 chicks which received the same diet supplemented with 2 per cent commercial cholesterol (Armour) and 5 per cent cottonseed oil (diet 2CO). About 7 chicks from each group were sacrificed on arrival, and at 1, 2, 3, 5, 7, 10, 12, 15 and 26 weeks of age.

The second series of 142 chicks used in this experiment was received Feb. 21, 1950, and divided at once into two groups similar to those of the first series. Animals of the second series were sacrificed at 8, 15, and 26 weeks. Some of these birds have been continued on the diets for longer periods. Because of some differences in results between the August and the February experiments, certain data from the two groups will be discussed separately.

Blood was drawn for plasma cholesterol determinations[2] at various intervals or at sacrifice. Chicks were examined postmortem for the presence of gross aortic atheromatosis and organ lipidosis. The general criteria for grading the degree of atheromatosis were those previously described.[3] However, in this series emphasis is placed on the gross grading of the thoracic aorta. The values obtained in the gross grading of the abdominal aorta are not added to the thoracic

aorta grades as heretofore. The gross specimens of the hearts and aortas were then stained with Sudan IV to bring out occult fatty infiltrations. The spleen, heart, liver and occasional other organs were examined microscopically in frozen sections using Sudan IV, or after fixing, paraffin embedding and staining with hematoxylin-eosin.

Results

Effect of 2CO Diet on Growth in the Newly Hatched Chick

Since there were no significant differences in the *rates of growth* in the August and the February series, these are treated together. The normal and the 2CO chicks had approximately equal feed intakes and gained weight at approximately the same rate (table 1). These results show that the 2CO supplements had no notable deleterious effect on the growth of the animal.

Table 1.—*Weight Gains and Feed Intake in Series 2 for Both 2CO and Control Groups*

Age (weeks)	Weight (Gm.)		Feed intake (Gm./week)	
	Control	2CO	Control	2CO
1	61	77	50	71
5	249	126	287	188
10	869	756	546	562
15	1730	1645	728	1128
20	1966	1985	657	688

In earlier studies from this laboratory[3, 4] chicks on a diet containing 2 per cent cholesterol and 20 per cent cottonseed oil were shown to be dwarfed. Since the chicks in the present experimental groups also received 2 per cent cholesterol, stunting of growth is probably not due to the cholesterol intake. It is likely therefore that the effect was due to the larger amounts of oil (20 per cent) which had been used in the earlier experiments with the idea of enhancing cholesterol absorption. It is known that raw cottonseed oil contains gossypol, a toxic yellow dye,[5] and it may have been that this compound was present in the oil used in earlier studies.

Plasma Cholesterol Levels at Various Age Periods

When the egg is laid, the egg white is nearly free of cholesterol; the yolk contains a cholesterol content of nearly 2 per cent which serves as building material during embryologic development. Little if any of the cholesterol is degraded during this period.[6] The yolk is enclosed within the abdominal wall shortly before hatching. At this time the plasma cholesterol level is about 300 mg. per 100 cc. Examination within the first few days reveals the remainder of the yolk sac in the process of absorption. The liver is grossly fatty, containing much intracellular sudanophilic material and numerous cholesterol crystals which are easily demonstrated by polarized light.

Ordinary Mash Diet. Chicks on the ordinary mash diet showed a rapid drop in plasma cholesterol levels from the natal 300 mg. per 100 cc. to an average of 90 mg. within the first week. No significant deviations from this value were observed throughout the 26 weeks of the experiment in this group (table 2).

Table 2.—*Plasma Cholesterol Levels (in mg. per 100 cc.) in Chicks on Regular Mash and 2CO Diets*

Age (weeks)	Series 1		Series 2	
	Control	2CO	Control	2CO
0	334	—	—	—
3	98	340	—	524
5	102	192	115	460
7	76	232	123	525
8	—	—	112	840
10	85	505	87	1467
12	91	820	93	926
15	66	872	110	1189
20	86	822	139	934
25	95	262	90	913

2CO Diet. In contrast to the control group, the August chicks placed on the 2CO diet maintained a plasma cholesterol level at 300 mg. per 100 cc. for the first eight weeks of life (table 2).

At the eighth week of life, despite the fact that there was no change in dietary or other regime, the cholesteremia showed a remarkable spontaneous increase to an average of 800 mg. per 100 cc. The new level was maintained over the course of the next 12 weeks. At about the twenty-second week, with the dietary regime continuing as before, the plasma cholesterol level decreased spontaneously to an average level of 260 mg. per 100 cc.

The February series of chicks behaved similarly to the August series described above except that the cholesteremia for the first seven weeks ranged somewhat higher, about 500 mg. per 100 cc. (fig. 1). The average plasma cholesterol level increased to about 800 mg. per 100 cc. at the ninth week, and to 1460 mg. per 100 cc. at the tenth week. The values then leveled off at an average of about 1000 mg. per 100 cc. (table 2) until about the twenty-fourth week when they fell to an average of 690 mg. per 100 cc. Several chicks maintained high cholesterol values at this time (1000 to 1800 mg. per 100 cc.) but the general tendency was toward a marked reduction (as low as 290 mg. per 100 cc.). A progressively greater number of chicks exhibited lower cholesterol values following the 24 week age period. Some of these chicks have been continued on a 2CO diet for longer periods of time, as previous experiments[10] have suggested that there may be a later endogenous elevation in the plasma cholesterol levels.

The remarkable changes in plasma cholesterol in the cholesterol-fed birds at 8 and at about 22 weeks, despite the unchanged dietary regime, strongly suggest that at these periods in the life of the chick, spontaneous changes occur in the endocrine and metabolic balance to influence the regulation of cholesteremia.

Data from Earlier Studies

Previous studies in this laboratory had shown unexplainable deviations in plasma cholesterol levels at various times during the course of the experimental work. These variations had been considered artefacts or to be due to unknown variations in feeding technic or sometimes attributed to technical error. It appeared advisable to review these data to determine if the unexpected variations could be related to the age of the animal.

Six groups of 2CO chicks with data which could be utilized for the present purpose had previously been studied in the laboratory. At the time of these experiments, we customarily purchased chicks at an approximate age of 3 to 5 weeks. For the purposes of the particular study under analysis at the time, some of the groups were kept in the laboratory for a week or more after arrival before the animals were placed on the 2CO regime. We therefore had available data on animals which were begun on the 2CO diet from 4 to 7 weeks of age.

An analysis of these records showed that regardless of the special experimental conditions being tested, a notable regularity could be seen in the pattern of the plasma cholesterol levels in five of the groups in that a marked rise in cholesteremia was seen at about the eighth week of life (table 3). These regimes, including ingestion of large amounts of thyroid powder or dinitrophenol[7] or removal of the pancreas,[8] had no significant effect on the appearance of the eight week effect. Two groups of 2CO chicks used as controls against these experiments also showed the hypercholesteremic response at about 8 weeks.

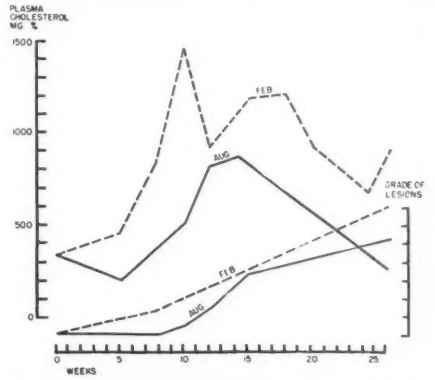

FIG. 1. Plasma cholesterol levels and grade of atheromatosis in the chick. The solid lines show the values for the chicks hatched in August. The broken lines represent chicks hatched in February. The upper two lines give average plasma cholesterol levels through the 26 week period. The lower two lines show the grading of the lesions found at autopsy in sacrificed animals at each period. The scale on the right is given in half-units (see text).

The Age Factor in Cholesteremia

In order to confirm and analyze the eight week phenomenon, the effect of the age at which the animals were placed on the 2CO diet was studied in a group of 28 chicks begun in February, 1950. These animals were divided into three groups. One of these groups was started on the 2CO diet at hatching, a second

was begun at 5 weeks, and the third group was placed on the 2CO diet at 7 weeks (fig. 2).

Eight animals placed on the 2CO diet at hatching showed an average plasma cholesterol of 524 mg. per cent at the third week of life and this value was maintained through the seventh week. In the eighth week, the average plasma cholesterol increased spontaneously to 840 mg. per cent; at the tenth week it was 1467 mg. per cent.

Eleven animals maintained on a plain mash diet for the first five weeks of life were begun on the 2CO diet at the fifth week. Within a week, the cholesteremia increased from the control values of about 90 mg. per 100 cc., to an average of 476 mg. per 100 cc.; at the tenth week of age (six weeks feeding) the cholesteremia averaged 1471 mg. per 100 cc.

The third group of 9 chicks was first given a normal mash diet for seven weeks and then placed on the 2CO diet. Within the first week of 2CO feeding the plasma cholesterol had risen to 644 mg. per 100 cc. At the tenth week of age (three weeks feeding) the average plasma cholesterol level was 1481 mg. per 100 cc.

Chicks maintained on normal mash had plasma cholesterols of about 90 mg. per 100 cc. throughout the entire 10 week experimental period.

These results demonstrate clearly that an endogenous change resulting in the upward regulation of the plasma cholesterol level occurs about the eighth week of life in the chick. This effect is independent of previous exposure to cholesterol or of the cholesterol level at 7 weeks. It is interesting to note that the eight week effect is not detected unless a hypercholesteremic stimulus is present, such as in chicks receiving a high cholesterol diet. No notable deviations of the plasma cholesterol level occur in chicks on a normal mash diet. This may account for the inability to evoke a hypercholesteremic response at various age intervals in the rabbit on a low cholesterol diet.[9]

Some time after the twentieth week, the plasma cholesterol unaccountably falls again (fig. 2). That this is not a permanent fall is indicated by previously published data on experiments carried on for 52 weeks,[10] in which the plasma cholesterol rose again after the temporary reduction at around 20 weeks.

TABLE 3.—*Plasma Cholesterol Levels (in mg. per 100 cc.) in Previous Experiments from this Department*

Regime	2CO	2CO	2CO dinitrophenol	2CO thyroid	2CO pancreatectomy	2CO pancreatectomy
Regime begun at week	7	5	7	7	5	5
Age at which observation made						
8	496	155	432	246	199	970
10	638	185	685	459	1288	1550
12	973	336	526	432	1140	1490
16	—	629	—	—	1225	—
17	999	—	617	292	—	1815
21	—	974	—	—	2605	—
22	420	—	290	436	—	974

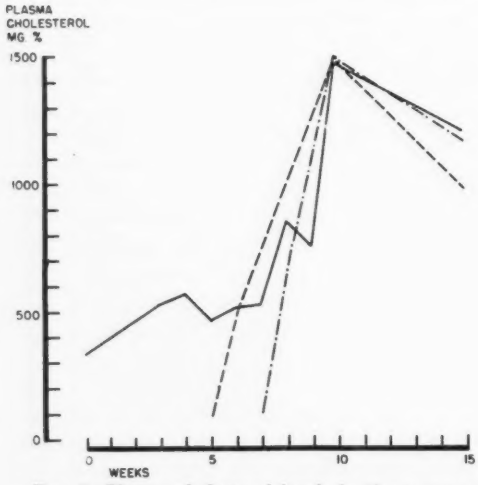

FIG. 2. Plasma cholesterol levels in three groups of baby chicks placed on 2CO diet at varying age periods : (–) were begun on 2CO diet at 1 day of age; (– –) were begun at 5 weeks and (–.–) at 7 weeks. Discussed in text.

Organ Lipidosis and Atheromatosis

Controls. Animals sacrificed on arrival at the laboratory (age 1 to 2 days) showed fatty livers but no arterial lipid infiltrations or atheromatosis, gross or microscopic. The fatty infiltration of the liver gradually disappeared and the liver took on a normal appearance over the course of the first two weeks in the animals on the plain mash diet.

In both the August and February animals receiving a normal mash diet, no thoracic, brachiocephalic or coronary lesions were observed at hatching.

In the grading system given below and in table 4, only the thoracic lesions are considered, since these are dependent upon cholesterol ingestion, while the abdominal lesions of the inter-renal region may occur in the absence of hypercholesteremia. Further, this inter-renal lesion is fundamentally a fibrotic process, with secondary lipid deposition when the animal is on a high cholesterol diet. By contrast, the thoracic lesions appear to be initiated as a result of intimal foam cell proliferation and this effect is closely correlated with cholesterol feeding and hypercholesteremia.

Gross lesions were seen in the abdominal aorta, below the renal arteries, at 12 weeks of age in these control animals. These were minimal lesions occurring in 3 of 15 animals, with an average grading of 0.5. The other 12 animals showed no gross lesions. Microscopic examination revealed the lesions to consist of slight thickenings of the intima with no lipid infiltration.

At 26 weeks, 6 of 15 control birds had abdominal aortic lesions averaging 0.75; moderate intimal thickening but no lipid infiltration was seen.

Cholesterol Enriched Diet (*Table 4*). In the group of animals begun in August 1949, no gross or microscopic lesions were seen through the time of the tenth week sacrifice. Beginning with the eleventh week, lesions were found in the thoracic aorta and in the brachiocephalic and coronary vessels in 2 of 4 birds. The percentage of animals with thoracic atheroma increased rapidly, and at 15 weeks of age all chicks autopsied were found to have atheromatosis.

The size and stage of development of the atheroma also progressed rapidly during this period, the average grade of the thoracic lesions being reported as 1.1 at 11 to 13 weeks, 2.1 at 15 to 18 weeks and 3.2 at 26 weeks. Despite extensive coronary atherosclerosis with virtual occlusion of many of the vessels, the myocardium showed no histologic damage.

At 26 weeks, large fibrotic plaques with calcium deposits, cartilage and bone formation were noted in the thoracic aorta. Fresh lipid deposits were seen marginally on the edge of these advanced lesions.

The series of animals begun on the 2CO diet in February (table 4) differed from that begun in August in that the cholesteremias were higher during the entire experimental period, and the tendency to atheromatosis was greater.

TABLE 4.—*Thoracic Lesions in 2CO Chicks*

August series				February series			
Weeks of age and on diet	Number sacrificed	Number with lesions	Grade*	Weeks of age and on diet	Number sacrificed	Number with lesions	Grade*
0 to 10	69	0	0	8	14	13	1.4
11	4	2	1.1	—	—	—	—
12 to 13	7	6	1.1	13 to 15	9	9	2.2
15 to 18	7	7	2.1	—	—	—	—
25 to 26	6	6	3.2	26	6	6	3.6

* Average of thoracic lesions in birds with lesions.

Most striking was the finding of gross thoracic atheroma graded as 0.9 in 2 chicks which died spontaneously at 5 weeks. Microscopically, several coronary arteries showed slight intimal lipid infiltration. Both brachiocephalic arteries showed large streaks of fatty infiltration in the intima and adjacent media. An interesting finding was marked splenic lipidosis with severe atheromatosis of the splenic arteries in these animals.

From the age of 8 weeks, all autopsied chicks of the February series had gross thoracic lesions and generalized atheromatosis. This became progressively more severe, being graded as 0.9 at 5 weeks, 1.4 at 8 weeks, 2.2 at 15 weeks and 3.6 at 26 weeks.

It can be seen from tables 2 and 4 that the February chicks did not show the resistance

to hypercholesteremia and atheromatosis which was seen during the first 8 weeks of life in the August chicks. The February chicks had earlier and more severe lesions early in life, although by the fifteenth week the degree of the lesions in the two groups was comparable (fig. 1).

These differences occurred despite the fact that the two series of animals were given the same diet at the same age periods. It may be that the summer chick is somehow different from the winter chick.

Discussion

Earlier studies from this laboratory demonstrated that the tendency to atherosclerosis may in general be correlated with the degree and duration of cholesterol feeding and therefore with the plasma cholesterol level.[3] However, the present findings make it clear that endogenous factors dependent upon the age period of the animal must also be considered if the tendency to atheromatosis is to be assayed. This effect of age is apparent during at least four periods in the life of the chick.

Thus, the chick lives its entire three weeks of embryonic life in a cholesterol rich environment. At the time of hatching, the plasma cholesterol level is about 300 mg. per cent and cholesterol can be discovered in large amounts in the liver and in other abdominal organs. Yet no atheromatosis or arterial lipid infiltrations are observed at this time. Whether the absence of atheromatosis in the embryo despite hypercholesteremia is due to resistance to this process or to other factors remains to be determined.

The hypercholesteremia seen at hatching falls rapidly to about 90 mg. per cent during the first week of life and remains at this level for the rest of the life of the animal, provided that excess amounts of this sterol are not ingested.

When the newly hatched chick is placed on a diet supplemented with 2 per cent cholesterol and 5 per cent cottonseed oil, a maintained cholesteremia ranging about 300 to 500 mg. per 100 cc. is seen in the course of the next eight weeks. Even the feeding of much higher percentages of cholesterol, done in the course of other experiments,[11] leads to no further increase in the cholesteremia in this age period.

It is during the first two months of life that we observed differences in the two series of experiments which were conducted. In our August series the plasma cholesterol level ranged about 300 mg. for the first two months. Serial studies up to the age of 7 weeks showed no lesions in the aortas or coronary arteries of these chicks. In the February group, however, a somewhat different course was seen in that the plasma cholesterol level ranged about 500 to 600 mg. per cent, and atheroma in the thoracic aorta, as well as in the brachiocephalic and coronary arteries were seen as early as 5 weeks of age. These lesions progressed and were moderately advanced by the time the animals were about 8 weeks of age. These seasonal variations are under further analysis.

At the eighth week of life of the chick, somatic changes manifest themselves in the beginnings of the rapid testicular growth corresponding to early puberty and the secondary rapid growth of the comb and changes in the feather patterns.[12] There is no evidence in the normal chick fed a regular mash diet to suggest that there are any changes in cholesterol regulation. However, in the 2CO animals and in subsequent series receiving as little as 0.25 per cent cholesterol supplementation of the diet[13] a change becomes apparent in a marked hypercholesteremia, levels approximating 1000 mg. per 100 cc. or more within the course of a week or so in the 2CO chicks.

The hypercholesteremia is maintained over the course of the next 12 weeks, a period of rapid somatic and testicular growth. During this period the tendency to atheromatosis increases markedly. This is seen in the fact that within four weeks after onset of 2CO feeding at the age of 8 weeks, the lesions and the plasma cholesterol levels are the same as in those animals receiving a cholesterol enriched diet from the time of hatching. The feeding of cholesterol during the first eight weeks is therefore much less effective in raising the plasma cholesterol level and in the production of atheroma than it is in the succeeding 12 weeks.

The degree of development of the lesions

was of the same order in the animals fed the 2CO diet since the seventh week of life, as in those begun on the diet immediately at hatching or at 5 weeks (table 4). Thus, despite the fact that the lesions began early in the group receiving 2CO since birth, the magnitude of the lesions in all groups was of the same order at the fifteenth week.

The occurrence of intimal proliferation, lipid infiltration and atheroma formation in chicks as young as 5 weeks of age argues strongly against the thesis that the arteriosclerotic process begins only on a site of preexisting vascular injury or in an aging artery. Inasmuch as the chick may live as long as 20 years[14] it can be seen that the 5 week period is but a very small part of the potential life of the animal. The development of atheromatosis during the second month of life can therefore not be attributed to a senility of the arterial tissues but must be considered as a pathologic process which may occur even in very young and presumably uninjured vessels.

The pathogenic role of increased cholesterol intake and hypercholesteremia is supported by the present results. The onset of the marked hypercholesteremia occurring at 8 weeks, followed by a rapid progression of lesions in the subsequent period further strengthens this argument. However, hypercholesteremia, per se, is not necessarily the only factor in atherogenesis, since the hypercholesteremia of the fetal period does not lead to arterial lipid infiltration and atheromatosis.

Despite the development of coronary lesions with a marked reduction in the lumen of the arteries in the chick, there have been no indications of significant myocardial injury. This protection of the myocardium against ischemia and necrosis may depend on the fact that the young chick myocardium is still capable of the elaboration of new vascular channels.

At the age of about 20 weeks the chick completes its normal growth and a second change in cholesterol balance is observed. The atherosclerotic process is considerably slowed down in its rate, and regression of lesions may occur at later periods in the life of the animal.

Our results clearly demonstrate that hypercholesteremia and atherosclerosis depend to a large extent upon the physiologic age of the animal. During certain periods in the life of the chick there is an increased tendency to hypercholesteremia and atherosclerosis, or perhaps a decreased resistance against this effect.

It is likely that these physiologic tides occur in animals other than the chick. For example, Pollack[9] has published data which suggest that rabbits younger than one year are less susceptible to atherosclerosis than older rabbits.

The comparative infrequency of atherosclerosis in children on high cholesterol diets has been used as an argument against the thesis that cholesterol ingestion predisposes to coronary atherosclerosis. The present results suggest that this age period may be one similar to the prepubertal resistance to atherosclerosis in the chick. A review of the literature of xanthoma tuberosum[15] shows that deaths have occurred in children with this disorder at the age of puberty (ages 10 to 15). Autopsy findings showed coronary atheromatosis. The tendency to xanthomatosis was probably present earlier in life, but did not become manifest in coronary artery disease until the age of puberty. This suggests the presence of mechanisms for the regulation of cholesteremia and atheromatosis in pubescent man similar to those seen in the chick at its pubertal age, 8 weeks.

In the literature, frequent occurrence of atherosclerosis in men in the fourth and fifth decades has been used in support of an aging concept in arteriosclerosis. On the basis of our present studies these results may be interpreted equally well as due to variations in the cholesterol tides depending on a changing endocrine balance, with a consequent decreased resistance to atherogenesis in this age period.

Rather than an aging of tissues, it appears that the physiologic period and the hormonal balance of the individual at a given time determines the tendency to atherosclerosis in the cholesterol-fed animal.

Summary

1. The problem of the relation of arterial aging and injury to the development of athero-

matosis was investigated by utilizing newly hatched chicks given a diet supplemented with 2 per cent cholesterol and oil (2CO).

2. Hypercholesteremia occurs in the chick during embryonic life. However, no atheromas were found in newly hatched chicks. This may be dependent on a specific resistance to atherogenesis during the prenatal period.

3. Atheromatosis was produced in the 2CO chick as early as the fifth week of life. These results cast doubt upon the concept that arterial aging and/or injury is a necessary precondition for the development of arteriosclerosis.

4. The facility with which hypercholesteremia and atheromatosis developed depended in large part upon the age period of the 2CO chick. Chicks were found to be generally resistant to hypercholesteremia and atherogenesis during the first 8 weeks of life.

5. At about 8 weeks of age, corresponding to early puberty, a spontaneous increase in the plasma cholesterol occurs when the animals are on a cholesterol enriched diet.

6. Atherogenesis procedes rapidly within the three to four weeks after the spontaneous rise in plasma cholesterol with the development of severe lesions by the twelfth week of life.

7. Spontaneous variations in the regulation of plasma cholesterol are also seen at about the twenty-second week, at the time of sexual maturation.

8. These experiments demonstrate that endogenous factors dependent upon the age period of the animal play a very important role in the regulation of cholesteremia and atherogenesis in the cholesterol-fed chick.

Acknowledgments

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References

[1] Lansing, A. I., Alex, M., and Rosenthal, T. B.: Atheromatosis as a sequel to senescent changes in the arterial tree. J. Gerontol. **5:** 314, 1950.

[2] Schoenheimer, R., and Sperry, W.: A micromethod for the determination of free and combined cholesterol. J. Biol. Chem. **106:** 745, 1934.

[3] Horlick, L., and Katz, L. N.: The relation of atheromatosis development in the chicken to to the amount of cholesterol added to the diet. Am. Heart J. **38:** 336, 1949.

[4] Dauber, D. V., and Katz, L. N.: Experimental atherosclerosis in the chick. Arch. Path. **36:** 473, 1943.

[5] Lillie, R. J., and Bird, H. R.: Effect of oral administration of pure gossypol and of pigment glands of cottonseed on mortality and growth of the chick. Poultry Sc. **29:** 390, 1950.

[6] Needham, J.: Biochemistry and Morphogenesis. Cambridge, University Press, 1942.

[7] Stamler, J., Silber, E. N., Miller, A. J., Akman, L., Bolene, C., and Katz, L. N.: The effect of thyroid and of dinitrophenol induced hypermetabolism on plasma and tissue lipids and atherosclerosis in the cholesterol-fed chick. J. Lab. & Clin. Med. **35:** 351, 1950.

[8] —, and Katz, L. N.: The effect of pancreatectomy on lipemia, tissue lipidosis and atherogenesis (spontaneous and cholesterol induced) in chicks. In press.

[9] Pollak, O. J.: Age and weight as factors in the development of experimental cholesterol atherosclerosis in rabbits. Arch. Path. **43:** 387, 1947.

[10] Horlick, L., and Katz, L. N.: Retrogression of atherosclerotic lesions on cessation of cholesterol feeding in the chick. J. Lab. & Clin. Med. **34:** 1427, 1949.

[11] Unpublished observations.

[12] Breneman, W. R.: A study of the pituitary-gonad-comb relationship in normal, unilateral castrate and caponized chicks. J. Exper. Zool. **114:** 115, 1950.

[13] Stamler, J., and Katz, L. N.: Production of experimental cholesterol induced atherosclerosis in chicks with minimal hypercholesteremia and organ lipidosis. Circulation **2:** 705, 1950.

[14] Mayand, N.: Longevité des oiseaux. In Traite de Zoologie **15:** 536, 1950.

[15] Rigdon, R. H., and Willeford, G.: Sudden death during childhood with xanthoma tuberosum. J. A. M. A. **142:** 1268, 1950.

An Exercise Test for Coronary Insufficiency

By DAVID LITTMANN, M.D., AND MELVIN H. RODMAN, M.D.

Any exercise tolerance test is intended to record the objective accompaniments of coronary insufficiency. The test must therefore be stressful to effect such insufficiency. Described in this report is an exercise test which is considered specific in demonstrating coronary inadequacy when present, and reliable in ruling it out, provided that the effects of tachycardia on the electrocardiogram are recognized.

ANGINA pectoris, literally a "pang in the breast," occupies a unique position among symptoms. Although still occasionally used to indicate any pain in the anterior chest, the term is more properly reserved for a sensation of specific type due to coronary artery disease. Despite its ominous implication, the term angina pectoris is sometimes applied to patients wholly on the basis of history and without objective evidence of heart disease. This may be justified when the symptom is characteristic, but serious errors in diagnosis may occur when the complaint is atypical. Pain in the chest may be due to any of a host of noncardiac conditions. Conversely, myocardial hypoxia may result in a sensation which the patient describes as breathlessness rather than pain. The discomfort may be otherwise atypical in character or distribution, and its relation to exertion inapparent or subtle.

As an aid in making the diagnosis of angina pectoris, special methods of study have been devised. These have all been based on the observation that electrocardiogarms made *during* angina pectoris were different from those obtained from the same patients between attacks.[1-4] This must be considered as the sine qua non in angina pectoris: *inadequacy of coronary circulation sufficient to produce pain must be reflected in simultaneous electrocardiographic changes.*

The adrenaline test[5] induces relative myocardial hypoxia by increasing cardiac work. While of value in many cases, the test is not without danger. Levine states, ". . . adrenalin injections are dangerous when given to patients who have heart disease and especially angina. This test, therefore, should never be employed when the diagnosis is quite definite . . ."[5] In the anoxia test of Levy and co-workers,[6] myocardial hypoxia is induced directly by exposing the subject to an atmosphere of diminished oxygen tension (10 per cent). This test, too, is attended with some danger. The exercise test, standardized and used most widely by Master and his associates,[7-10] uses a more physiologic method of demonstrating coronary inadequacy, namely the familiar exercise of walking over stairs.

The object of all these tests is to provoke a state of myocardial hypoxia sufficient in degree to result in angina pectoris and/or diagnostic electrocardiographic changes. This will occur in susceptible individuals—patients with coronary inadequacy. Conversely, where no coronary insufficiency is present the test will be negative.

THE TEST

For some years we have employed a variation of the Master two step test which, in our opinion, has demonstrated a high degree of specificity. Like the original test it consists of walking over a platform having two 9 inch steps. It is employed only in those patients who have *no objective evidence of heart disease* by physical examination, x-ray and by conventional resting electrocardiogram. Where the history indicates that the complaint is more commonly experienced at some particular hour of the day the test is performed at that

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time. If no such temporal factor is elicited the test is always run in midafternoon following a medium or large noon meal. In order to provide a constant and easily reproducible cold stimulus[2] the patient performs the exercise while holding in each hand approximately 4 ounces of gauze-wrapped ice. The exercise is carried out at the patient's own rate except when this proves to be unusually slow or fast. Under those circumstances a metronome adjusted to sound 60 beats to the minute is employed to regulate the pace. The patient is instructed to take one step at each beat and allow two beats for turning. A complete single trip can thus be made in six seconds: two seconds up, two seconds down, two seconds for the turn. The patient is instructed to turn in opposite directions alternately to minimize the tendency to vertigo. The subject walks over the steps until he experiences pain or until he is forced to stop by dyspnea or fatigue. Failing this the test is continued until 100 single or 50 round trips have been completed.

A six lead record consisting of leads I, II, III, V_2, V_4, and V_5 is made before beginning and upon completion of the test. (In a few instances, additional leads are made as well.) The limb lead electrodes are left on during the exercise so that it is possible to make the second electrocardiogram immediately. This is not ordinarily done, however, until the pulse rate has slowed to 100 per minute or less.

Interpretation. In the interpretation of the test we rely entirely upon the electrocardiogram. If no electrocardiographic changes occur the test is considered to be negative. (This holds whether or not pain occurred or 100 trips were completed.) When significant electrocardiographic alterations appear the test is considered to be positive. Occasionally, the procedure may have to be stopped very early because of leg pain, dyspnea, or arbitrary unwillingness of the patient to continue. Such tests, fortunately rare, are classified unsatisfactory.

In interpreting the tracings obtained after exercise it has not been found necessary to set up rigid quantitative criteria. The positive tests are unequivocally positive, with well defined and easily seen changes from the control tracing. These consist of extensive S-T depressions, T wave reversals, or both. In all instances, these may be seen in more than one lead, particularly in the precordial positions.

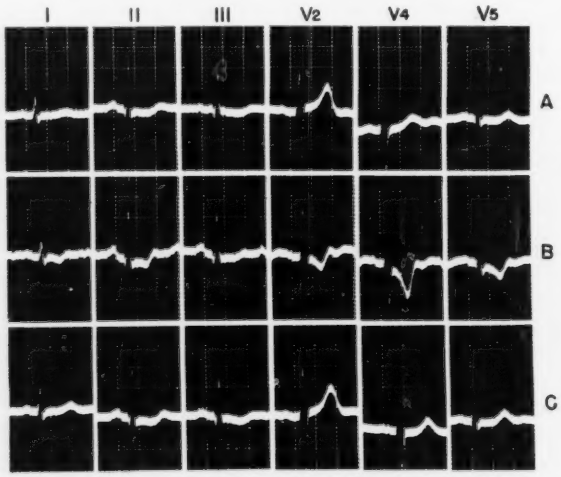

FIG. 1. Exercise tolerance test of a 40 year old white male truck-driver. *A*. Control tracing immediately before exercise. *B*. Record obtained after 34 trips over two step course. *C*. Tracing made 10 minutes after exercise.

This illustrates the similarity of the ST-T changes (of V_4 and V_5 in *B*) to those seen in left ventricular strain. This patient has subsequently suffered an episode of coronary occlusion.

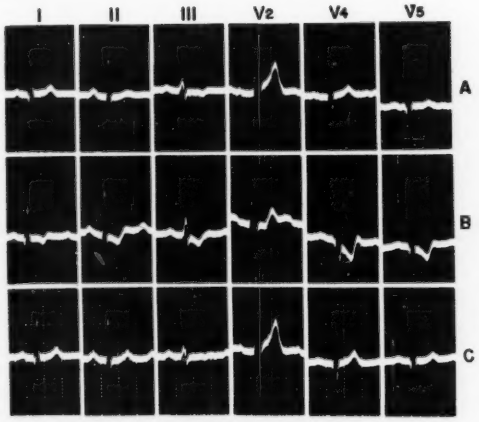

FIG. 2. Exercise test of a 53 year old white male with atypical chest pain. *A*. Control tracing. *B*. Tracing made after 60 trips over two step course. *C*. Record obtained 10 minutes after exercise.

The S-T sloping and asymmetric T-wave inversion seen in *B* resemble closely the changes characteristic of left ventricular strain.

precordial leads of patients with left heart strain (figs. 1 and 2). It appears likely that acute left ventricular strain actually results from the test and that this phenomenon is reflected in the electrocardiogram.

False Positive Tests. Unfortunately, other electrocardiographic changes are also observed which may serve as the basis for misinterpretation of exercise tests. T wave lowering and/or S-T segment depressions may occur in individuals with normal hearts following exercise and during tachycardia. Both of these manifestations may be present immediately following physical effort of the magnitude employed in this study (fig. 3).

The mechanism underlying the changes seen during tachycardia has been best elucidated by Ashman[11] using the schema of Nahum and Hoff. Briefly stated, tachycardia, however induced, alters the recovery period of the myocardium. This so changes the relationship

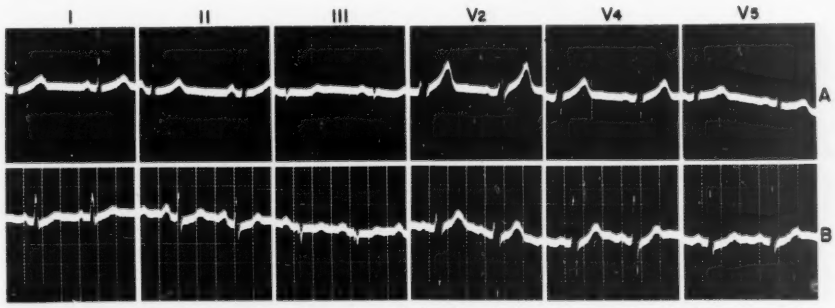

FIG. 3. Record of a 36 year old white male with duodenal ulcer. This patient had no complaints resembling angina pectoris and was used as a control subject in a study of angina suspects. *A*. Control tracing before exercise. *B*. Record obtained after 100 trips over standard exercise course, during which the patient suffered no discomfort. In this tracing are seen S-T depressions in II, III, and the chest leads of a degree which might be erroneously interpreted as evidence of coronary insufficiency.

We have not encountered S-T elevations (except in aV_R), P-R prolongation, QRS delay, premature beats or other arrhythmias. This may be due to the fact that the test has not been performed by patients with otherwise demonstrable heart disease.

A striking similarity is apparent between some of the records obtained after exercise and those characteristic of left ventricular strain. The asymmetrically inverted T waves with downward sloping of the S-T segments appear identical with those seen in the left

of the postulated monophasic components of the electrocardiogram that S-T depression and T wave lowering or inversion may occur.

In our experience, the magnitude of the alterations due to tachycardia is trifling when compared with the gross abnormalities which occur with coronary inadequacy. In this regard, Ashman[11] has stated, "In using the exercise or anoxia test for coronary insufficiency, an appreciation of the causes of normal deviations is desirable. It is true of the published records (for example, the paper by Twiss and Sokolow)

that the changes are undoubtedly significant and not to be explained by a physiologic change. . . . But in less expert hands, *especially when there is considerable acceleration* and when the R or S waves are large, *a wholly unspecific change might easily be regarded as significant.*" (Italics ours.)

In order to minimize these distracting phenomena, we delay making the test electrocardiogram until the pulse rate has slowed to

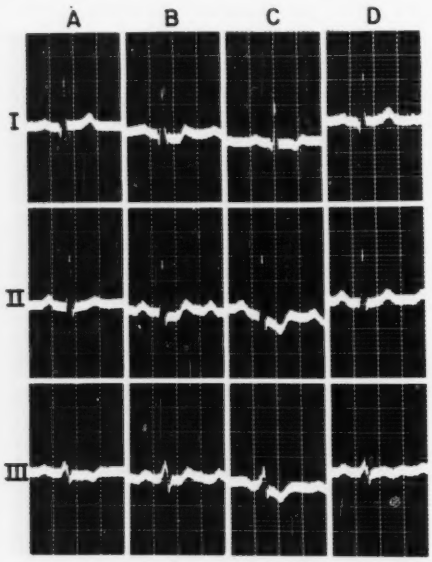

FIG. 4. Exercise tolerance test of a 40 year old white male. *A*. Control tracing. *B*. Record obtained two minutes after exercise. *C*. Record obtained five minutes after exercise. *D*. Record obtained 10 minutes after exercise. (For the sake of convenience, only the standard leads are shown.)

Although definite abnormalities are present in *B*, the record made five minutes after exercise shows still more striking changes. By 10 minutes after exercise, the tracing had reverted to normal.

100 per minute or less. This generally occurs within two to four minutes. Whenever tachycardia persists beyond this period, a tracing is started at four minutes and repeated one or more times until the cardiac rate has diminished to below 100. In no instance has it been our observation that electrocardiographic changes resulting from coronary insufficiency disappear in so short a period. Indeed, it has been suggested that in some cases the diagnostic abnormalities may not become apparent until some minutes after the completion of exercise.[12, 13]

In figure 4 is illustrated a similar situation. Although definite changes are present in tracing B, made immediately after exercise, the tracing made five minutes later shows more marked and extensive abnormalities.

Previous reports have indicated electrocardiographic changes which did not persist beyond a few minutes after exercise.[2] However, the records illustrating these alterations all had rates of well over 100. The deviations in those records were such as may be seen normally during tachycardia. When the criteria for significant changes consist of minute numerical deviations (as is true in some exercise tests), the results of tachycardia may well be sufficiently widespread and of such magnitude as to constitute false positive tests.

False Negative Tests. False negative tests may occur if the test situation is not stressful enough to provoke characteristic symptoms. We have already mentioned that the test is performed at that time of day when the patient reports angina is most apt to occur. The addition of a constant cold stimulus also increases the likelihood of a positive test. That these accessory factors are important was illustrated by a 56 year old man whose intermittent chest pain suggested angina pectoris. However, the pain was of varying character, not particularly related to effort and was said to last 30 minutes to several hours. The physical examination, x-ray and resting electrocardiogram were all normal. An exercise tolerance test was performed and concluded at 52 trips because of the onset of pain. The test tracing, however, demonstrated only slight lowering of T waves and minute S-T depressions. The test was repeated the following morning and was halted after 60 trips because of dyspnea and fatigue. The electrocardiogram at this time was entirely normal and unchanged from the control record. The patient then volunteered the information that his spontaneous pain occasionally radiated to the teeth. This was so suggestive that a third test was made, this time in mid-afternoon after a generous lunch. On this occasion the patient completed only 45 trips and stopped because of the onset of pain. The electrocardiogram made on this occasion was

grossly abnormal and is shown in figure 5. The tracing obtained 10 minutes after exercise was once more normal and similar to the control electrocardiogram.

It will be noted that this patient was able to accomplish a fair amount of exercise on each occasion. In our experience the amount of exercise which could be accomplished by different patients with angina pectoris varied widely. Occasionally individuals could perform only 12 to 15 trips before the onset of pain. Others did not stop until they had made as many as 60 trips. Most patients with coronary disease, however, complained of symptoms between 25 and 40 complete single trips. This illustrates

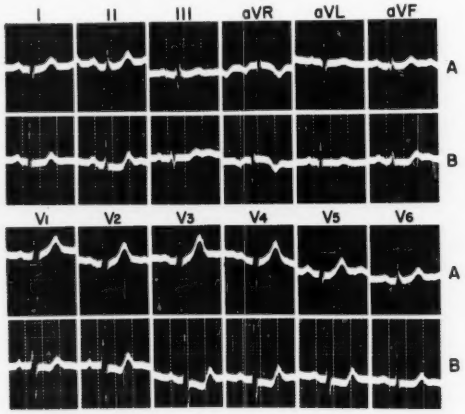

FIG. 5. Exercise test of a 56 year old white male. *A*. Control tracing. *B*. Record obtained after 45 trips over two step course. For discussion, see text.

the importance of allowing the exercise to proceed until the onset of complaints. Exercise sufficient to provoke symptoms and electrocardiographic changes in one individual of given age and weight may be entirely inadequate for another similar patient. Some standardized tests, however, require the performance of a specified amount of work dependent upon age and weight. To avoid false negative tests under these circumstances, it becomes necessary to attach significance to minute and possibly nonspecific deviations from the control tracing. It should be recalled that the exercise tolerance test is merely a graphic record of an episode of myocardial hypoxia. It follows, therefore, that this cannot be obtained in the absence of stress sufficient to provoke hypoxia.

This concept may be illustrated by figure 6. Myocardial hypoxia may be assumed to occur some time after the start of exercise and to increase until the onset of pain, when the physical effort is terminated. The conventional exercise test seeks to demonstrate the presence of myocardial hypoxia at point A, some time after its onset but before it becomes sufficient to produce symptoms. However, there is no assurance that point A regularly occurs after any arbitrary amount of exercise. That the "double two step" has been resorted to reflects the uncertainty that must attend such technic. On the other hand, B, the point where the rising curve of myocardial hypoxia intersects the threshold of pain, is always easily identified. It is at this time that we make our tracings. The amount of exercise between the start of

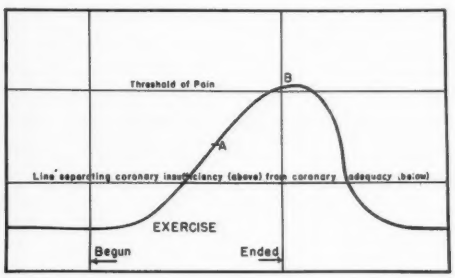

FIG. 6. Diagrammatic representation of angina pectoris induced by effort.

the test and point B varies with the individual patient but is relatively unimportant since we are concerned only with the end point.

For this reason, we have not, for all practical purposes, set a limit to the number of trips a patient is asked to perform. We feel that the 100 trip end point is not important in itself since the great majority of patients with coronary inadequacy will develop symptoms long before they reach this limit.

Criticism may be directed against the employment of stressful and possibly hazardous testing in individuals with possible coronary disease. It is emphasized, therefore, that the test as described is employed only in angina suspects who lack objective evidence of heart disease. We consider that patients exhibiting cardiac enlargement alone or together with important hypertension or valvular disease

may well suffer from angina pectoris. Such patients require no exercise tests. Similarly, individuals with electrocardiograms showing patterns of bundle branch block, myocardial infarction or heart strain should not be subjected to effort tests. Conversely, it is likely that patients without cardiac enlargement or abnormal electrocardiograms have relatively less heart disease and may be safely tested. No untoward incidents have occurred in the performance of numerous tests and none is anticipated.

A subsequent communication will demonstrate the usefulness of this test in a group of 169 angina suspects.

Summary and Conclusions

Electrocardiograms obtained during episodes of angina pectoris are observed to be different from records made on the same patients between attacks. Based on this observation, special tests of coronary adequacy have been devised, among which is the exercise test. In this paper is described a modification of the two step test which differs from the usual procedure in the following particulars:

1. In appropriate instances, it is performed at that time of day when the patients customarily experience angina. In the remainder, it is done following meal times.
2. A constant cold stimulus is applied.
3. No practical limit is set to the amount of exercise performed.
4. The effects of tachycardia upon the electrocardiogram are recognized and the test so performed that these distracting changes may be avoided.
5. It is not performed on patients with objective evidence of heart disease.

These modifications are based on the following rationale: The exercise tolerance test, to be adequate, must provide sufficient stress to induce coronary insufficiency in susceptible patients. It is therefore undesirable and contrary to the purpose of the test to impose arbitrary limitation to the amount of exercise performed. False negative tests may be produced in this fashion. In interpreting the electrocardiograms obtained after exercise, the effects of tachycardia must be considered. Unless these changes are recognized and steps taken to avoid them, false positive tests may be obtained, especially if the criteria for significant change are minute numerical deviations.

The possible danger of stressful testing of individuals with possible coronary artery disease is recognized. It is for this reason that the test is not carried out by any patients with objective evidence of heart disease.

References

[1] Wood, F. C., and Wolferth, C. C.: Angina pectoris: the clinical and electrocardiographic phenomena of the attack and their comparison with the effects of experimental temporary coronary occlusion. Arch. Int. Med. **47:** 339, 1931.

[2] Riseman, J. E. F., Waller, J. V., and Brown, M. G.: The electrocardiogram during attacks of angina pectoris: its characteristics and diagnostic significance. Am. Heart J. **19:** 683, 1940.

[3] Wilson, F. N., and Johnston, F. D.: The occurrence in angina pectoris of electrocardiographic changes similar in magnitude and in kind to those produced by myocardial infarction. Am. Heart J. **22:** 64, 1941.

[4] Rundles, F. S., and Friedkin, N. F.: Electrocardiographic alterations resembling those produced by myocardial infarction observed during spontaneous attack of angina pectoris. Ann. Int. Med. **28:** 671, 1948.

[5] Levine, S. A.: Clinical Heart Disease. Philadelphia, W. B. Saunders Company, 1945.

[6] Levy, R. L., Bruenn, H. G., and Russell, N. G., Jr.: The use of electrocardiographic changes caused by induced anoxemia as a test for coronary insufficiency. Am. J. M. Sc. **197:** 241, 1939.

[7] Master, A. M., Friedman, R., and Dack, S.: The electrocardiogram after standard exercise as a functional test of the heart. Am. Heart J. **24:** 777, 1942.

[8] — and Oppenheimer, E. T.: A simple exercise tolerance test for circulatory efficiency with standard tables for normal individuals. Am. J. M. Sc. **177:** 223, 1929.

[9] —: The electrocardiogram and "two-step" exercise; a test of cardiac function and coronary insufficiency. Am. J. M. Sc. **207:** 435, 1944.

[10] —, and Jaffee, H. L.: Electrocardiographic changes after exercise in angina pectoris. J. Mt. Sinai Hosp. **7:** 629, 1941.

[11] Ashman, R.: The normal human ventricular gradient. IV: The relationship between the magnitudes A_{QRS} and G, and the deviations of the RS-T segment. Am. Heart J. **26:** 495, 1943.

[12] Twiss, A., and Sokolow, M.: Angina pectoris: significant electrocardiographic changes following exercise. Am. Heart J. **23:** 498, 1942.

[13] Froment, R., Blondet, P., and Gallavardin, L.: Les signes électrocardiographiques de l'angor coronarien à propos de 211 observations récentes. J. de méd. de Lyon No. 621, 1945.

Pressure Curves from the Right Auricle and the Right Ventricle in Chronic Constrictive Pericarditis

By A. Tybjaerg Hansen, M.D., P. Eskildsen, M.D., and H. Götzsche, M.D.

Characteristic patterns of the pressure curves from the right auricle and the right ventricle have been found in chronic constrictive pericarditis by various investigators. It has been uncertain, however, whether or not the findings were pathognomonic, and whether they were reliable pictures of the pressure conditions or artefacts. Consequently the views upon the underlying mechanism have been different too. It is concluded from the studies here presented that the pressure curves are pathognomonic when in their most pronounced form, and that they are not artefacts and thus furnish a proper basis for inferences as to the hemodynamics in chronic constrictive pericarditis.

PRESSURE recording from the accessible sections of the heart and great vessels by means of the catheterization technic has proved an important aid in the diagnosis of different types of congenital heart disease. Generally speaking the same is not the case in acquired heart diseases. However, as a deviation from that rule, chronic constrictive pericarditis seems to give rise to a very characteristic pattern of the pressure curves from the right auricle and the right ventricle.

Earlier Publications

Pressure curves from a case of constrictive pericarditis from Cournand's laboratory were published by Bloomfield and associates[1] in 1946. The peculiarities of the tracings as compared with normal findings were emphasized. Wood and co-workers[2] at the Mayo Foundation have also published pressure recordings from a patient suffering from constrictive pericarditis. The unusual tracings from the ventricle were, however, explained as artefacts resulting from too low a natural frequency of the pressure recorder. Recently, Eliasch, Lagerlöf and Werkö[3] have demonstrated the characteristic pattern of the pressure curves in 3 cases of adhesive pericarditis.

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Presented in part before the Twenty-Third Annual Scientific Sessions of the American Heart Association, San Francisco, June 22–24, 1950.

In an earlier publication[4] we presented briefly our experiences with constrictive pericarditis and mentioned the probable diagnostic value of the pressure recording from the right auricle and the right ventricle in such cases. Since then we have had an opportunity to make some additional observations which may serve to elucidate the functional basis of the characteristic findings.

Methods and Material

The pressure recordings were the essential part of the studies. They were made by means of an electric condenser manometer constructed by one of us.[4] Its dynamic properties when connected to the heart catheter were known and adapted so that artefacts of consequence for the present studies could be excluded. The midaxillary line was chosen as zero line. The electrocardiogram was recorded simultaneously. In some cases the phonocardiogram was recorded at the same time as the pressure measurement. The time marking interval was 0.1 second, subdivided in some of the tracings into 0.02 second intervals. Ordinary x-ray examination and x-ray kymograms of the heart were made in all cases.

Our material comprises 6 clinically classic cases of chronic constrictive pericarditis (P. M. J. f. 155/47; M. C. f. 951/48; G. L. K. f. Vp. 714/48; C. A. S. m. 411/49; S. G. m. 27-10-10/49; N. C. L. m. 1118/49). One of them (N. C. L. m. 1118/49) was operated upon and examined postoperatively also. A seventh patient (L. S. P. f. 1112/49) had presented a typical syndrome before operation which was performed prior to the present studies. Only postoperative studies were made in this patient. In one additional case (P. S. m. 860/48) the diagnosis was suspected but could not be made with certainty on the basis of the results obtained by means of

ordinary methods of examination. To these cases is added for comparison one case (E. A. m. 547/49) of effusive pericarditis.

Results

The pressure recordings from the 6 typical cases showed quite similar patterns and can be satisfactorily represented by the curves shown in figure 1. They were obtained from a 45 year old woman (G. L. K. f. Vp. 714/48) who had had symptoms for at least five years. There were engorged veins, enlarged liver, moderate ascites, fairly marked edema of the legs and exertional dyspnea. At the left sternal border a pronounced pericardial click was audible. X-ray examination showed the heart to be only slightly enlarged (ratio 16:30), and to a wide extent covered by a solidly calcified pericardium. Nonetheless the part of the border of the heart represented by the left ventricle showed almost normal movements throughout the heart cycle. The movements of the right auricular and right ventricular boundaries, however, were much restricted.

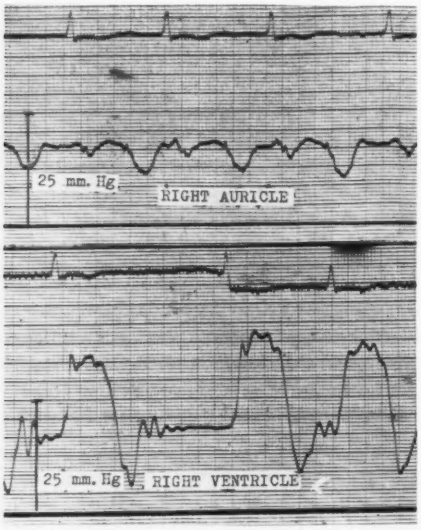

Fig. 1. Upper tracing: auricular pressure curve. Lower tracing: ventricular pressure curve. The electrocardiogram is at the top of each tracing. From a 45 year old female (G. L. K. f. Vp. 714/48) presenting a typical syndrome of constrictive pericarditis. The M form of the auricular curve and the diastolic dip in the ventricular curve are well marked. Respiratory variations of the ventricular systolic and diastolic pressures are practically equal so that the pulse pressure in the ventricle is almost unchanged regardless of irregular heart rate. (ECG shows auricular fibrillation.)

The *auricular* pressure curve is characterized by a higher maximum pressure than the normal one and by equal heights of the two plateau-like maxima. The minimum pressure (corresponding to the minimum in the ventricle) does not reach the zero level as is the case normally. The mean pressure is, therefore, relatively more elevated than is the maximum pressure. The electrocardiogram shows that auricular fibrillation is present so that the form of the curve must largely depend on other factors than the contractions of the auricle.

The *ventricular* pressure curve shows a maximum pressure which is slightly elevated but not definitely outside the normal range. The descending part of the curve runs a normal course except that the pressure does not fully reach the zero line even though it comes more closely to it than does the auricular minimum pressure. Having reached its minimum, however, the pattern differs very markedly from normal findings, as the pressure rises steeply to a level roughly midway between maximum and minimum pressure where it forms a plateau which is not changed until the onset of systole. In the presented case there are very pronounced pressure oscillations located in the first part of the diastolic plateau. Their frequency is not high enough for them to be audible. The most conspicuous finding, the diastolic dip, may be found in other cases, even in normal ones, but is never of a relative magnitude comparable with that found in constrictive pericarditis, as far as could be concluded from the present material.*

That the diastolic dip is not a consequence of an elevated venous and auricular pressure is well known from measurements in other types of congestive heart failure. This is illustrated in figure 2 (J. P. O. m. 928/49). The *auricular* pressure is very elevated, yet the

* Recently we have observed a case in which a fairly marked diastolic dip was present, though the minimum pressure was far from reaching the zero line. On autopsy a chronic myocarditis with an unusually widespread and high degree of fibrosis was found.

tracing shows no M-form. The *ventricular* diastolic dip is only vaguely indicated. The diastolic pressure is much higher than normal.

Our experiences with other forms of pericarditis are limited to one case of tuberculous, exudative pericarditis. The *ventricular* curve (shown in figure 3) differs from both the normal pressure curve and that found in chronic constrictive pericarditis. Most conspicuous seems to be the marked diastolic oscillations in conjunction with a steadily rising pressure throughout diastole.

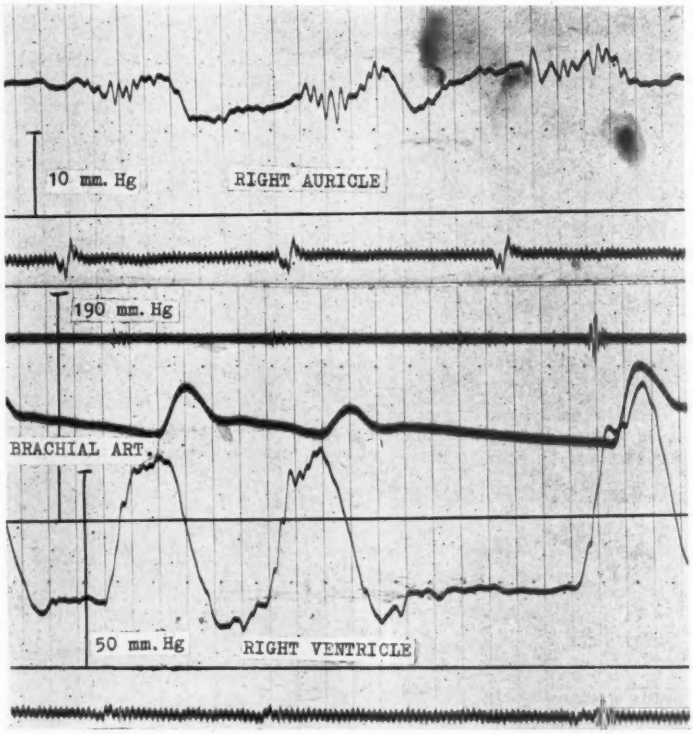

FIG. 2. Upper tracing: auricular pressure curve. Lower tracing: ventricular pressure curve. The electrocardiogram is the lower curve in both tracings. In the lower tracing phonocardiogram and femoral arterial pulse curve are also shown. From a patient (J. P. O. m. 928/49) suffering from cardiac failure with elevated venous pressure but no pericardial constriction. It is noted that the auricular pressure and the diastolic ventricular pressure are at a high level. No "constriction pattern" is visible. ECG shows auricular fibrillation.

The Effect of Operation on the Pressure Curve in the Right Auricle and Ventricle

The direct proof of the causal relation between the pericardial constriction and the pressure curves presented here as being characteristic is given in the case that was examined before and after pericardiectomy. The patient was a 21 year old man (N. C. L. m. 1118/49) with a typical syndrome. There was no systolic retraction of the ictus which was palpable in the fourth intercostal space. A marked pericardial click was heard at the left sternal border. X-ray examination showed normal size of the heart (ratio 14:34). The pericardium was not calcified. Kymography revealed restricted movements of all borders of the heart. On operation the pathologically modified pericardium was removed except that portion covering the left auricle. The innermost part was much like granulation tissue. No calcification was found. The total thickness of the pericardium was 8

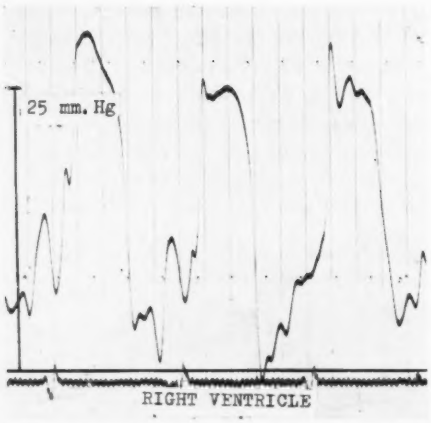

FIG. 3. Ventricular curve from a 25 year old male patient (E.A. m. 547/49) with a tuberculous effusive pericarditis. ECG at bottom of the tracing. Note the very marked oscillations in diastole. No diastolic plateau.

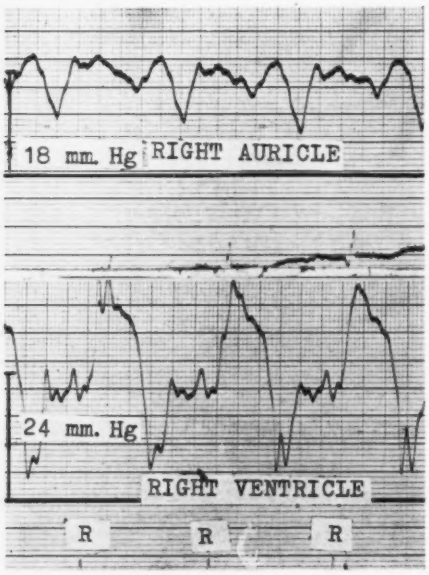

FIG. 4. Upper tracing: auricular curve. Lower tracing: ventricular curve. Only a portion of the electrocardiogram is shown in the upper tracing. From a 21 year old male (N.C.L. m. 1118/49) with typical chronic constrictive pericarditis. The pressure record was obtained before operation and shows the typical "constriction pattern."

mm. Only the sixth rib was resected. The patient, who was in poor condition before the operation, recovered completely clinically and returned to normal life, showing no restricted physical activity whatsoever.

Figure 4 shows the same type of *auricular* and *ventricular* pressure curve as in the first case of constrictive pericarditis (fig. 1). The tracings from the control examination one year after the operation (fig. 5) show that the dip has completely disappeared and that the pressure curves are practically normal. Concurrently with the change of the pressure curve the kymographic picture had shifted to a picture which could not be distinguished from a normal one. As was the case before the operation fluoroscopy showed little or no movements of the heart on changing the position of the body.

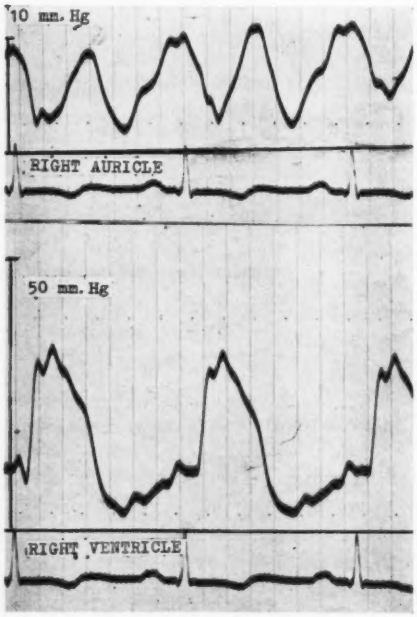

FIG. 5. Upper tracing: auricular curve. Lower tracing: ventricular curve. From the same patient illustrated in figure 4 but recorded 12 months after successful pericardiectomy. The typical "constriction pattern" has disappeared.

In the case that was only examined postoperatively the tracings show normal or almost normal configuration. The patient was a 25 year old female (L. S. P. f. 1112/49) on whom

pericardiectomy was performed 11 years earlier. Clinical and roentgenologic signs almost completely disappeared soon after the operation. She was admitted to the hospital because of ascites and pleural effusion. She was febrile with widely fluctuating temperature. Her symptoms had reappeared rather acutely. The pressure curve from the right *ventricle* is shown in figure 6. Although not entirely normal it does not display the characteristics of a constriction curve. It is notable that the minimum pressure reaches the zero line. The auricular

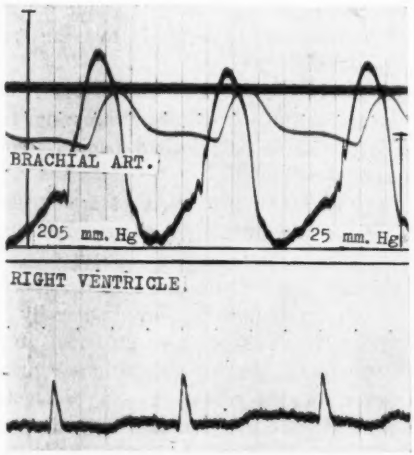

FIG. 6. Right ventricular curve from a 25 year old female (L.S.P. f. 1112/49) 11 years after successful pericardiectomy for chronic constrictive pericarditis. The curve is not pathologic. The examination was made because peritoneal and pleural effusions had reappeared in connection with spiking temperature. (See text).

maximum pressure was less than 10 mm. Hg. Thus the result of pressure recording did not support the diagnosis of renewed constriction of the heart as the reason for her effusions. Rather, together with the fever and the fact that she recovered on treatment with dihydrostreptomycin, it pointed towards a flare-up of her (tuberculous?) polyserositis.

DISCUSSION

The consistent finding of characteristic right auricular and ventricular pressure curves in patients presenting the classic syndrome of chronic constrictive pericarditis suggests on a purely empiric basis that pressure measurements in uncertain cases may be of some diagnostic help. This has already been referred to above in a "negative" case, and is further illustrated by the curves in figure 7 from a case (P. S. m. 860/48) in which clinical and roentgenologic criteria were not decisive. The curves, although not as impressive as, for example, the curves in figures 1 and 4, support the diagnosis of constriction. Furthermore, as a means of evaluating the result of operation, pressure measurement may be useful (fig. 5). Whether the unusual deflections in the pressure curves are artefacts or not affects the above conclusions very little. This question must be an-

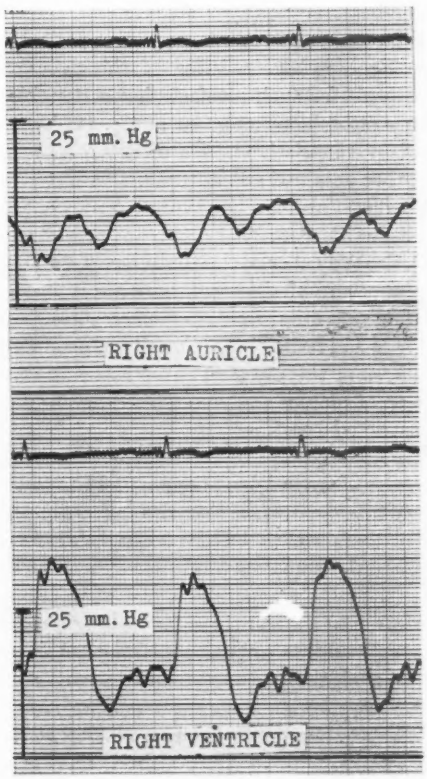

FIG. 7. Auricular and ventricular pressure curves from a 44 year old male (P.S. m. 860/48) suspected of having chronic constrictive pericarditis with very slight symptoms. The curves support the diagnosis.

swered, however, prior to any attempt to correlate the peculiar pattern with the hemodynamics in chronic constrictive pericarditis.

Against the form of the pressure curves being due to artefacts are the following:

(1) The frequency response in the manometer-catheter system used in the present studies was suitable.[4] (2) Poor frequency response would not account for an elective occurrence of the curve pattern in constrictive pericarditis. (3) Bending and twisting of the catheter as the basis for such artefacts is not tenable for the same reasons as given in (2). (4) The fact that in constrictive pericarditis typical recordings are obtained on electrokymography[5, 6] and on ballistocardiography[7] very strongly suggests that there is also a characteristic pressure curve. (5) The typical curve has been recorded directly by puncture of the right ventricle in one case during operation (see later comments).

We feel justified, therefore, in explaining the changes in the pressure curve as being due to essential factors governing the function of the constricted heart.

In accordance with the generally accepted concept expressed by Chevers in 1842 (quoted by White[8]), we consider the hampered diastolic dilatation to be the main factor in the abnormal hemodynamics. This view is supported by the comparable effect of the normal pericardium as shown in heart-lung preparations[9, 10] and in animal experiments[11] as well as by clinical experiments with patients suffering from chronic constrictive pericarditis.[12]

The systolic contraction of the heart is in our opinion relatively unimpaired. That means that the (right) ventricle is emptied as completely as in normal cases or at least almost so, so that the static pressure at the end of systole drops to almost normal values. Hereby is created a steep pressure gradient between the auricle and the ventricle. As a result blood rushes from the auricle into the ventricle which rapidly reaches its maximum distention, which is limited by the constricted pericardium. This explains the sudden rise in pressure. At the time the pressure has reached the diastolic level again the diastolic filling has been completed. The ventricular systolic pressure seems, in the presence of irregular heart action, to be much less dependent upon the duration of the preceding diastole than usual, provided diastole lasts longer than the diastolic dip. As mentioned in the description of figure 1, the diastolic dip is followed by smaller oscillations. Although most conspicuous at the beginning of the diastolic level, they are detectable in the upstroke of the dip (fig. 4). They are presumably a result of the water-hammer–like action of the blood against the rigid wall of the heart. Their low frequency causes them to be inaudible, but it seems reasonable to believe that the proto- or middiastolic gallop (pericardial click) which so often is heard in cases of chronic constrictive pericarditis is caused by the same phenomenon.

The pressure curve from the *auricle* reflects the events in the *ventricle*. The minimum pressure lags 0.01 to 0.02 second behind that of the *ventricle*.

In our explanation of the pressure curves in constrictive pericarditis we have not found it necessary to assume that an elastic recoil of the thickened pericardium and/or the thoracic wall plays any important part. Physically it is also difficult to imagine such an effect on the basis of surgical and pathologic observations. Moreover, recent studies in a case* of constrictive pericarditis during surgical operation have shown that the early diastolic dip may be present under circumstances where no elastic effect of the pericardium and the thoracic wall is possible. The pressure curves that are shown in figure 8 were recorded by puncture of the heart wall with a 25 gage needle directly connected with the manometer. This system has a natural frequency of about 90 cycles per second and is properly dampened.

Due to the difficulties of localizing the right ventricle before stripping the pericardium, only pressure curves from the left ventricle were obtained at this stage of the operation. After an adequate pericardiectomy had been performed pressure curves were recorded from both ventricles. The right ventricular curve showed the typical constriction pattern al-

* We are indebted to Dr. Alfred Blalock, Department of Surgery, The Johns Hopkins Hospital, for permission to include this case in our material.

though the diastolic dip was a little broader than that found preoperatively on heart catheterization.

At first glance this result appears somewhat confusing; however, the persistence of the dip was in conformity with the direct observation that a sharp diastolic arrest was still present, resulting from paper-thin inelastic strands left on the surface of the heart. Postoperative studies by means of heart catherization will show whether or not the ventricular pressure curve will revert to normal as in other cases. A gradual stretching of the remaining strands is not at all improbable. The fact that in some cases clinical recovery requires a certain time to be completed[13] may suggest such a mechanism.

The interpretation of the pressure curves given above suggests that more than qualitative diagnostic information might be obtained from the appearance of a certain curve. A well pronounced diastolic dip almost reaching the zero line should indicate a remarkable degree of constriction in conjunction with a well functioning myocardium. In such cases a good result of pericardiectomy should be expected, all other conditions being equal. If the diastolic dip is relatively less prominent and the pressure rise begins farther from the zero line we have reasons to assume that a certain degree of "myocardial insufficiency" has entered the picture. Such curves are predominantly found in cases of chronic constrictive pericarditis with large hearts.

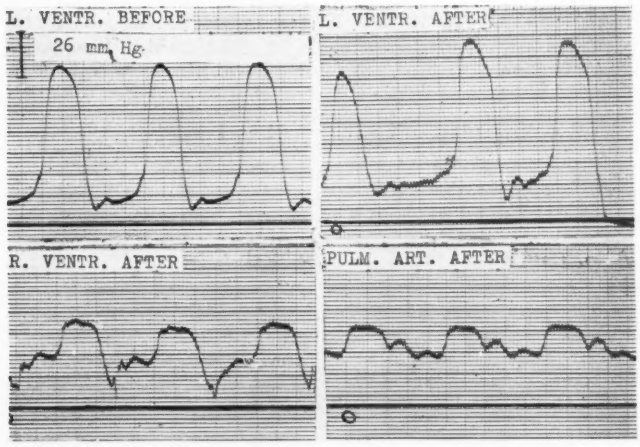

FIG. 8. Pressure curves from left ventricle, right ventricle and pulmonary artery obtained by puncture (25 gage needle) during thoracotomy. Zero line = midaxillary line. Upper curves: left ventricle before and after stripping the heart. The systolic pressure is slightly higher after the pericardiectomy. Lower left curve: right ventricle after removal of pericardium. The early diastolic dip is still present. (See text.) Lower right curve: pulmonary artery. The later part of diastole is on the same level, and reveals the same pattern, as the pressure curve of the right ventricle in the corresponding part of the heart cycle. An early diastolic dip is absent in the pulmonary curve in this particular case.

SUMMARY

(1) The existence of characteristic patterns of the right *auricular* and the right *ventricular* pressure curves in chronic constrictive pericarditis has been confirmed by the findings in 6 classic cases.

(2) It is demonstrated that the curves may revert to normal following pericardiectomy.

(3) It has been shown, partly by direct recordings from the heart during operation, that the typical findings on heart catheterization are not likely to be artefacts.

(4) An explanation of the peculiar patterns of the pressure curves is presented.

(5) The diagnostic value of the findings is discussed.

REFERENCES

[1] Bloomfield, R. A., Lauson, H. D., Cournand, A., Breed, E. S., and Richards, D. W., Jr.: Recording of right heart pressures in normal subjects and in patients with chronic pulmonary disease and various types of cardio-circulatory disease. J. Clin. Investigation **25:** 639, 1946.

[2] Wood, E. H., Geraci, J. E., Pollack, A. A., Groom, D., Taylor, B. E., Pender, J. W., and Pugh, D. G.: General and special technics in cardiac catheterization. Proc. Staff Meet. Mayo Clin. **23:** 494, 1948.

[3] Eliasch, H., Lagerlöf, H., and Werkö, L.: Diagnos av adhesiv pericardit med särskild hänsyn til hjärtkatetrisering. Nordisk Med. **44:** 1128, 1950.

[4] Hansen, A. T.: Pressure measurement in the human organism. Dissertation, Teknisk Forlag, Copenhagen, 1949; Acta Physiol. Scandinav. **19:** Suppl. 68, 1949.

[5] Gillick, F. G., and Reynolds, W. F.: Electrokymographic observations in constrictive pericarditis. Radiology **55: 77,** 1950.

[6] McKusick, V.: Electrokymography in the diagnosis of chronic constrictive pericarditis. Twenty-Third Annual Scientific Sessions, Am. Heart A., San Francisco, June 22–24, 1950.

[7] Scarborough, Wm. R.: Personal communication.

[8] White, P. D.: Heart Disease, ed. 3. Macmillan, 1947.

[9] Kuno, Y.: The significance of the pericardium. J. Physiol. **50:** 1, 1915–16.

[10] —: Contributions to the physiology of the pulmonary circulation. J. Physiol. **50:** 140, 1915–16.

[11] Carleton, H. M.: Delayed effect of pericardial removal. Proc. Roy. Soc. London, s.B. **105:** 230, 1930.

[12] Lyons, R. H., and Burwell, C. S.: Induced changes in circulation in constrictive pericarditis. Brit. Heart J. **8:** 33, 1946.

[13] Mortensen, V., & Warburg, E.: Chronic constrictive pericarditis. Acta med. scandinav. **131:** 203, 1948.

Advanced Disturbances of the Cardiac Mechanism in Potassium Intoxication in Man

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The use of the artificial kidney at the Peter Bent Brigham Hospital in the treatment of acute renal shutdown has afforded a unique and extensive opportunity to study the disturbances of rhythm and conduction occurring in potassium intoxication. In this theoretic, and at times frankly speculative, paper the authors present evidence which suggests the applicability to man of Wiggers' views based upon animal experimentation, namely that the ectopic rhythms developing in this condition arise "by default" (escape mechanisms) rather than "by usurpation" (increased excitability) and that potassium exerts its early and preponderant effect upon the subendocardial layers of the human ventricle.

THE VARIOUS arrhythmias developing during the course of potassium poisoning have interested many observers. Sinus slowing, [1-4] sinus arrhythmia, auricular standstill, auriculoventricular block,[2, 3, 5, 6] auricular fibrillation,[6-9] ectopic ventricular beats,[7] ventricular tachycardia,[1, 6, 7] ventricular fibrillation[2, 3, 6, 7] and ventricular standstill[1, 2, 5, 6, 10, 11] have been reported. First degree heart block has been a common finding. Although in the pre-electrocardiographic era higher grades of auriculoventricular block had been mentioned[3] and are reported to have occurred once in a canine experiment,[10] they have not been noted in man. Since the P waves are apt to become lost because of their prolongation and the decrease in their amplitude, and because they may be engulfed in the preceding ventricular complex,[4] their recognition, and accordingly the recognition of the higher grades of auriculoventricular block, is difficult if not impossible. By the same token it is exceedingly difficult under the circumstances to distinguish between sinus arrhythmia and auricular fibrillation. While there is no question about the common occurrence of sinus slowing and arrhythmia when the P waves are still easily recognized, a grossly irregular rhythm recorded when the P waves are absent or are no longer recognized with certainty as such, could be due as well to sinus arrhythmia with persistent sinus activity as to auricular fibrillation. A third but less likely explanation for the irregular ventricular rhythm might be auricular standstill with arrhythmia of the ventricular pacemaker.

The disturbances in the ventricular mechanism developing during potassium intoxication have been even more puzzling to physiologists. Two curious sets of observations have demanded explanation. These are: (1) the inception of ectopic rhythms while the organism is under the influence of a substance whose physiologic effect has long been regarded as an inhibitor of the myocardium and (2) the development of ventricular tachycardia or fibrillation under certain circumstances associated with potassium excess and their inhibition under other conditions associated with potassium excess.

Hering[7] and later Nahum and Hoff[4] sought to explain these apparent discrepancies by assuming the simultaneous operation of two differing effects of potassium on cardiac receptors. Thus Hering[7] postulated a primary

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The study was conducted while J. P. M. was a research fellow of the American Heart Association and W. S. was Travelling Fellow in Cardiology, British Postgraduate Medical Federation (University of London).

inhibitory action upon the so-called normotopic centers (sinus slowing, auriculoventricular block and intraventricular block) and a stimulating influence upon the so-called heterotopic centers (extrasystoles, paroxysmal ventricular tachycardia, ventricular fibrillation). Without assuming different types of receptors Nahum and Hoff[4] pointed out that whereas potassium, if infused slowly, produces widespread inhibition of cardiac automaticity culminating in complete standstill, it may, if infused rapidly, enhance cardiac automaticity. They regarded the development of foci of increased automaticity in the presence of intraventricular block as resulting in the incoordination which is ventricular fibrillation. MacWilliam,[12] on the other hand, attributed a purely depressive effect to potassium, emphasizing that, in conditions of depressed conduction, stimuli not faster than rates commonly seen when the heart is beating in coordinated fashion, may cause fibrillation. Wiggers, Theisen and Shaw[13] maintained that potassium depresses conduction, first in the bundle branches and internal layers of the ventricle, and subsequently in diverse portions of the myocardium; incoordination follows when some fractions escape complete inhibition, but total cessation occurs when all portions of the myocardium are completely depressed.

It has been suggested that a study of the earlier stages preceding the onset of potassium fibrillation might cast some light upon its mechanism. Hering considered ventricular premature beats an essential preliminary. Nahum and Hoff found no extrasystoles but observed widening of the QRS complex and changes in the S-T segment and in the T wave as forerunners of fibrillation. Wiggers and associates noted sinus slowing and depression of auriculoventricular conduction as constant findings; instances of premature ventricular beats (perhaps actually ventricular escape) were present in some but by no means all of their experiments. They concluded that premature beats are an incidental phenomenon and not an essential prelude to fibrillation.

It is quite generally agreed that intraventricular block is an important feature of all but the very earliest stages of potassium intoxication. The question has arisen whether: (1) this disturbance in transmission of the impulse is limited to the specialized conducting tissue of the heart; (2) all myocardial tissue, ventricular muscle proper, bundle branches and subendocardial Purkinje network alike, are involved indiscriminately; (3) conduction is first impaired in the bundle branches and subendocardial fibers, then in other parts of the ventricular myocardium,[13] or (4) there is a diffuse interference with spread of the wave of excitation, with the cells of the conduction system being more susceptible to potassium excess than the rest of the heart.[14]

In the normal heart the beginning of the QRS complex corresponds to the beginning of activation of the ventricular muscle proper, more particularly that of the septum. Conduction in the bundle branches and in the subendocardial Purkinje tissue is actually included in the P-R interval. But conduction is normally so extremely rapid in these tissues that it does not last long enough to be registered as a visible part of the P-R interval. Accordingly, the time consumed in the bundle branches is not represented in the normal electrocardiogram. The prolongation of the QRS complex in the bundle branch block is actually due to unidirectional activation of the interventricular septum and eccentric excitation of ventricular muscle proper. The diagnosis of bundle branch block is made rather upon the inferential evidence of an abnormal delay in the electrical activation of one ventricle or the other.[15] The literature contains very little evidence for bundle branch block in potassium poisoning. Experimental studies, in the manner of Lewis, of the heart poisoned with potassium have not yet been reported. Hence, although we know that the P-R interval is prolonged in hyperkalemia, it is not known just how much of the P-R interval represents transmission of the impulse in the bundle branches. In one canine experiment Nahum and Hoff[4] found that at an advanced stage of potassium intoxication the left ventricle contracted 0.05 second before the right ventricle. Conceding the existence of diffuse intraventricular block these authors concluded that right bundle branch block was also present. Finch and co-workers,[16] recognizing the gross resemblance between the tracings of

bundle branch block and the biphasic potassium curves, applied the criteria of Wilson to the study of the bipolar chest leads in potassium poisoning. They were unable to confirm the existence of bundle branch block and concluded that the changes could more logically be ascribed to general impairment of conduction throughout the heart. In the experimental animal pure bundle branch block is rarely associated with a duration of the initial ventricular complex exceeding 0.12 second by more than a few hundredths of a second. If this figure is greatly exceeded, as it is apt to be in the more advanced stages of potassium intoxication, the conduction defect cannot be explained by the bundle branch block alone; it is then necessary to assume a greater or lesser degree of impaired conduction in the ventricular muscle proper.

With these considerations in mind it is our purpose in this paper to present observations on six cases of potassium intoxication in which advanced disturbances of the cardiac mechanism were recorded. These cases were culled from a total experience at this writing with 30 hyperkalemic patients. Other aspects of 3 of them (cases 1, 3 and 4) have been described in another communication.[17]

Case 1. Ventricular escape, flutter, tachycardia and fibrillation: auricular fibrillation in potassium intoxication. J. M. C., PBBH #9A41, a South American newspaperman with chronic rheumatic valvular heart disease was admitted in uremia on Oct. 19, 1948. The only abnormality in the admission electrocardiograms was low electromotive force. The first three weeks of his hospitalization were characterized by evidences of severe acute infection and nitrogen retention. On November 13 there was an abrupt and striking change in his appearance. He developed a flaccid paralysis which began in his legs and spread to his arms and apparently involved the muscles of respiration. Electrocardiograms (fig. 1) recorded at this time were quite typical of potassium intoxication. The ventricular rhythm was slightly irregular, the rate 74 beats to the minute. The QRS complexes were bizarre and broad, measuring 0.16 second in duration. There were deep, wide negative deflections (usually S waves) in the conventional leads and in the unipolar chest leads. The T waves were tall and pointed, especially in leads V_{3-5}. In leads V_{3-6} the segment leading from the nadir of the S wave to the peak of the T wave was an almost straight line. P waves were recorded in lead III but were much more clearly visible in lead V_1. A continuous recording of lead II with the direct-writing electrocardiograph was commenced at 12:10, when further disintegration of the ventricular complexes was observed (fig. 2*A*). The QRS interval now measured approximately 0.28 second and the trace was in almost continuous motion, the rhythm was quite regular, and the heart rate 115 beats to the minute. At this point, the serum potassium level was 9.8 mEq./L. At 12:45 (fig. 2*B*) the rate of the heart slowed appreciably, the rhythm became grossly irregular again and the ventricular complexes somewhat sharper, the QRS complex measuring 0.16 second (fig. 2*C*). At 12:53 the trace abruptly developed a continuous

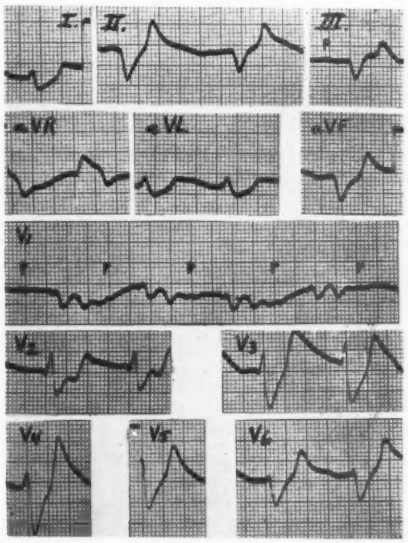

FIG. 1. Case 1. Electrocardiograms characteristic of potassium intoxication showing sinus slowing and sinus arrhythmia with broad, low P waves in lead III and more sharply defined P waves in lead V_1. The ventricular complexes present decreased R waves, increased S waves, depressed RS-T segments and, especially well seen in leads V_3 to V_6, smooth sloping curves from the nadir of the S to the apex of the tall pointed T waves.

sinusoidal appearance (fig. 2*D*) resembling that described in the electrocardiographic literature as characteristic of ventricular flutter. The rate was 155 beats to the minute. At this point an intravenous infusion containing 75 Gm. of glucose with 35 units of crystalline zinc insulin in 500 cc. of water was commenced.* During the first few minutes of this infusion, this continuous motion of the baseline persisted but the complexes became somewhat

* The rationale of the various forms of therapy employed in this study is described in detail in the companion publication.[17]

sharper, now resembling more closely the complexes of ventricular tachycardia. The rate of the heart increased to 184 beats to the minute (fig. 2*E*, *F*).

cent solution of sodium chloride containing 5 units of insulin was infused. The ventricular complexes became sharper and the rate slowed to 90 beats to

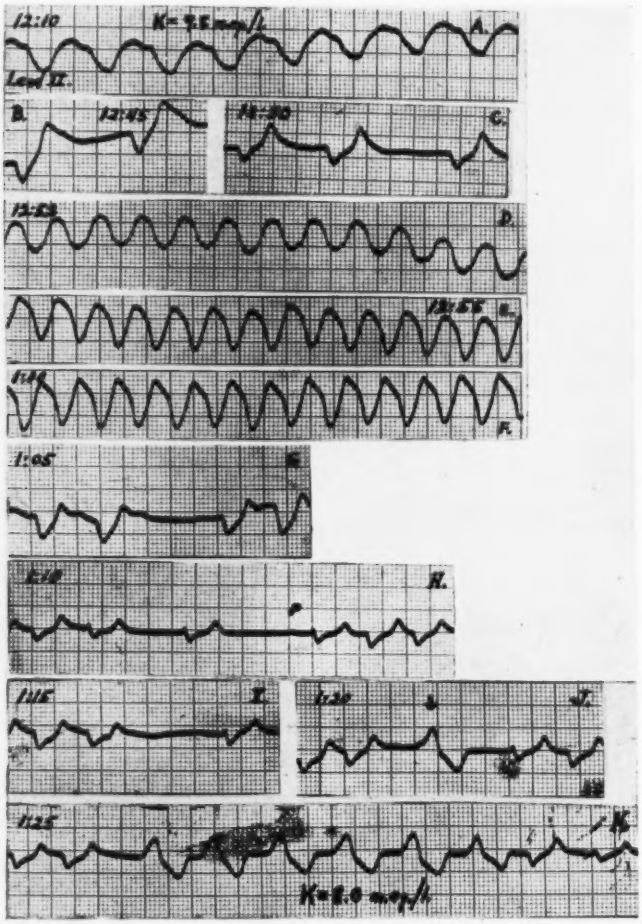

FIG. 2. Case 1. Fragments of continuous recording of lead II. *A*. Regular rapid rhythm (rate 115) showing further disintegration of the ventricular complexes. *B*. Thirty-five minutes later showing return to appearance noted in figure 1. *C*. Same five minutes later. *D*. Ventricular "flutter" at rate of 155; glucose-insulin infusion begun at this point. *E*. Ventricular "tachycardia" at the rate of 180 during glucose-insulin infusion. *F*. Same at rate of 184; glucose-insulin infusion continued. *G*. Return to appearance noted in *C*; glucose-insulin continued. *H*. Following sodium chloride and insulin showing shortening of QRS complex and return of P waves with sinus arrhythmia. *I*. Same at completion of saline-insulin infusion. *J*. Ectopic ventricular (escape) beat shortly after the beginning of normal saline infusion. *K*. A series of such beats beginning as escape mechanism; rate before sequence 140, during sequence 107.

Toward the end of the infusion the complexes again resumed (fig. 2*G*) approximately the form they had at 12:50. Shortly after this, the glucose-insulin infusion having been completed, 500 cc. of 3 per

the minute (fig. 2*H*) but intraventricular block persisted. In this strip a small oscillation was recorded, probably representing auricular activity (a small P wave is noted in the long pause preceding the third

complex from the end of the strip). At 1:15 when the saline-insulin infusion had been completed, there was very little further change in the appearance of the tracing (fig. 2*I*). At about this time infusion of 150 cc. of physiologic solution of sodium chloride was begun. Shortly afterward an ectopic beat was recorded (indicated by arrow in fig. 2*J*) with a configuration opposite the other complexes in that lead. This beat was not premature but developed rather after a long pause, suggesting an escape mechanism. In strip 2*K* a succession of such beats was recorded, again beginning as an escape mechanism rather than prematurely. Furthermore the ventricular rate during this salvo of ectopic beats was slower than the ventricular rate previous and subsequent to the "paroxysm." It is of some interest that the same type of broad ventricular complex was inscribed whether the ventricle was activated in the usual or in an opposite direction.* This suggests a diffuse slowing in ventricular activation regardless of the point of origin of the impulse. Here, then, was a sequence of six ectopic ventricular beats beginning as an escape or release phenomenon.

Figure 3*A* represents the complete set of tracings (of which figure 2*K* is lead II) taken at 1:25 following the completion of the infusion. At this time the patient had received a total of 22.6 Gm. of sodium chloride, 87.5 Gm. of glucose and 40 units of crystalline zinc insulin. The serum potassium had fallen from 9.8 mEq. per L. before the infusion to 8.0 mEq. per L. after the infusion. The QRS complex measured 0.14 second, the S waves were deep, T waves in precordial leads were still tall and pointed but P waves were not visible. In short, although there had been some improvement in the appearance of the complexes, they still showed characteristic changes of potassium intoxication.

The patient's blood was then dialyzed by the artificial kidney (hemodialysis) over the course of three hours. With the transfusion administered in the course of this dialyzing procedure, the patient received another 6 Gm. (approximately) of sodium chloride. When the dialysis was concluded, the serum potassium level had fallen from 8.0 to 5.7 mEq. per L., and the electrocardiogram showed striking improvement, the only remaining changes of hyperkalemia being minimal pointing of the T waves in leads V_{2-4}, low voltage in the limb leads and irregularity of the ventricular rhythm.

The patient received digitalis for the first time after the last postdialysis tracing was recorded. Hence, none of the changes produced up to this point can be attributed to digitalis. During the six hours following the commencement of digitalization the ventricular rate slowed to normal; within the next 12 hours the tracings exhibited normal sinus rhythm, the P-R interval was at the upper limits of normal (0.20 second), the ventricular rate was 85 beats to the minute but low voltage persisted in the limb leads. One day later the tracings were unchanged. It is apparent that the changes induced by the artificial kidney persisted for 48 hours despite the lack of any treatment other than digitalis.

During the subsequent week the patient's clinical state was precarious and observations on the relative efficacy of various chemical forms of treatment and of hemodialysis were carried out. These are

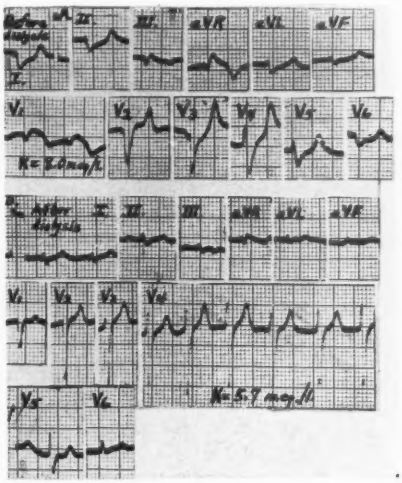

FIG. 3. Case 1. *A*. Complete set of tracings following infusions showing persistent changes of potassium intoxication. Note sharp pointing of the T waves. *B*. Same following artificial kidney showing disappearance of all changes except low voltage and emergence of grossly irregular rhythm, probably auricular fibrillation. The T waves are still pointed.

described in case 1 of the collateral study[17] and are not relevant to the present discussion. A second dialysis (one week after the first) was followed by a slight transitory improvement, but after a day or two his condition deteriorated progressively and for the first time a pericardial friction rub was heard. Tracings taken on the third day showed first degree block (P-R interval 0.24 second), intraventricular block (QRS 0.11 second) and low electromotive force. The following evening he developed nausea and vomiting and at 9 p.m. complained of numbness in the arms. At 10:15 he became quite excited. At 10:30 the biceps reflexes could not be elicited. Tracings taken shortly thereafter (figure 4) resembled those obtained at the onset of potassium

* Wilson and Herrmann[18] commented upon this same striking broadening of the ventricular premature beats occurring in a patient with terminal uremia and oliguria, attributing this peculiar form to a "toxic" depression of the conductivity of the Purkinje system.

intoxication (fig. 1) showing intraventricular block (QRS 0.28 second), auricular standstill and a gross irregularity of the ventricles. The ventricular complexes in the standard limb leads became progressively smaller and finally presented irregular undulations resembling coarse ventricular fibrillation. After a few minutes the baseline was virtually at a standstill and the patient died. Postmortem examination showed chronic rheumatic mitral and aortic valvulitis with superimposed subacute bacterial endocarditis, acute myocarditis and pericarditis and focal embolic glomerulonephritis.

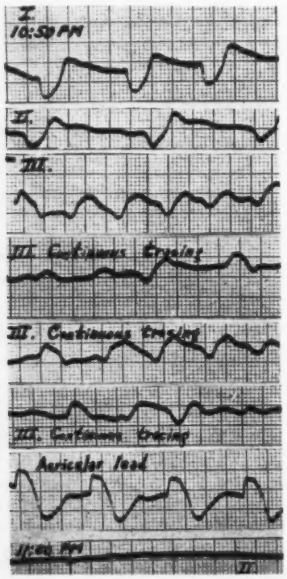

FIG. 4. Case 1. Terminal tracings shown in order in which taken. The first four strips show bizarre complexes with slow rate (66 in lead II) and irregular rhythm. Portions of the fourth and sixth strips show ventricular fibrillation. The final strip shows ventricular standstill.

Case 2. Terminal mechanism in potassium intoxication: "ventricular flutter" and ventricular standstill. J. Z., PBBH #6B988, a 32 year old man, was admitted because of oliguria, mellituria and jaundice complicating excision of a parotid tumor performed six days previously at another hospital. Examination showed jaundice, slight generalized abdominal tenderness, a palpable liver, clouding of the sensorium and a large subconjunctival hemorrhage. Electrocardiograms showed tall pointed T waves characteristic of hyperkalemia but there were no physical signs corresponding to this finding. The serum potassium level was 7.4 and the serum sodium 130 mEq. per L., the nonprotein nitrogen 275 mg. per cent, total protein 5.7 Gm. per cent and serum bilirubin 1.32 mg. During the next three days until the patient's death, a number of different treatments were exhibited and electrocardiograms were taken frequently, but in spite of temporary remissions, he went downhill rapidly. Necropsy showed lower nephron nephrosis, severe acute pulmonary edema, a normal heart and petechial hemorrhages in the bowel wall ("uremic colitis").

Figure 5 illustrates serial electrocardiograms (lead II) taken during the 15 minute period preceding death. The first three (short) strips show progressive disintegration of the ventricular complex with prolongation of the QRS complex from 0.36 to 0.40 second and of the Q-T interval to 0.18 second. In the first long strip there is recorded, following a long pause, a series of oscillations with alternating tall and smaller peaks. The crude resemblance of each pair of peaks to the ventricular complexes recorded earlier suggests that they correspond respectively to the initial (depolarization) and final (repolarization) deflections. The absence of an isoelectric interval between the complexes and their over-all contour are reminiscent of the pattern of auricular flutter. This phenomenon continues through the next two (continuous) strips but the rate increases and the smaller peaks become less and less conspicuous and finally vanish so that an appearance was eventually recorded much more nearly like that of figure 2*D* of the preceding case. The fourth long strip, recorded less than a minute later, shows a flat plateau interrupted irregularly by broad sinusoidal troughs. The four long strips thus far recorded can be regarded as perhaps manifesting different variations of so-called "ventricular flutter." In the following strip (8:53:48) a period of ventricular standstill lasting 5.6 seconds is recorded between two of the same type of disorganized sinusoidal ventricular complexes. The next strip (8:54:42) followed one minute 24 seconds of ventricular standstill with a smooth baseline. The progressive changes from larger, relatively regular and smoother undulations to smaller, coarser and quite irregular undulations are clearly shown in the next three strips which are continuous with this. Whether the last of these tracings represents ventricular standstill or fibrillation is difficult to say; if it is standstill, the waviness of the baseline is in marked contrast to the smoothness of the baseline recorded at 8:53:48. The complexes of the final strip, which followed four minutes and nine seconds of asystole with the same type of wavering baseline just described, resembled "monophasic action currents" with relatively rapid upward deflections and slow, smooth, rounded returning deflections. This series of beats, not entirely reproduced, lasted 18 seconds, successive ventricular deflections showing a progressive rounding off until the paroxysm ended abruptly with ventricular standstill. Occasionally monophasic ventricular complexes, singly

or in pairs, were recorded thereafter, but soon became less and less frequent and finally failed to appear.

cases, the operation of anoxia through the intermediation of electrolytic changes is an open field for investigation.

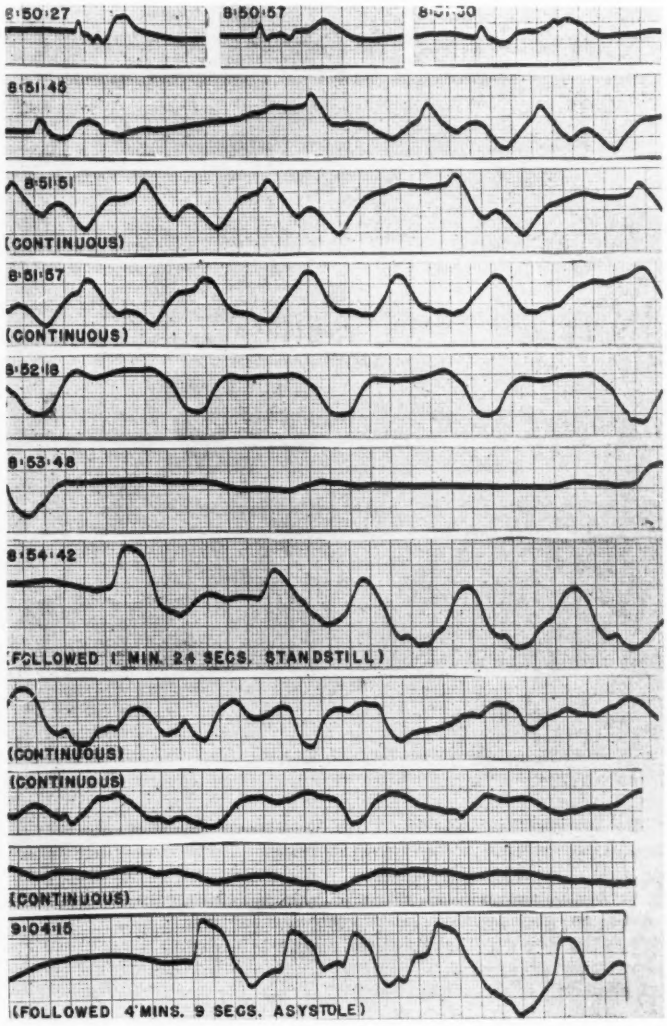

FIG. 5. Case 2. Terminal mechanism in potassium intoxication. Complete set of tracings completed at 8:50 a.m. was characteristic of advanced potassium intoxication with auricular standstill, pronounced intraventricular block, bradycardia, irregular ventricular rhythm and pointed T waves in the precordial leads. Serial recordings of lead II are here illustrated showing possible variations of "ventricular flutter" in the first four long strips, ventricular standstill in the fifth (8:53:48) and in the beginning of the final (9:04:15) strips, and a wavering baseline in the next to the last strip.

Although, since these were terminal tracings, the role of anoxia cannot be eliminated, it should be emphasized that the serum potassium level on the day of death was 10 mEq. per L. Indeed, in certain

Case 3. Auricular fibrillation and idioventricular rhythm in potassium intoxication. B. E., PBBH #5B345, a 68 year old man, was admitted to the hospital on June 29, 1949, because of a hemolytic

reaction and renal shutdown following a transurethral prostatic resection. A detailed description of the clinical, chemical and electrocardiographic observations is presented in our other paper[17]; for present purposes the sequence of changes recorded in lead V_5 is reviewed. Figure 6*A*, recorded shortly after admission, showed bizarre broad QRS complexes occurring at the rate of 136 beats to the minute. P waves could not be recognized. The ventricular rhythm was regular. At first sight the strip had the appearance of ventricular tachycardia. However, in ventricular tachycardia the rhythm is generally slightly irregular and abrupt in onset. This diagnosis is not favored here because the rate increased gradually rather than suddenly and the ventricular complexes had a similar appearance when the rate was slower.

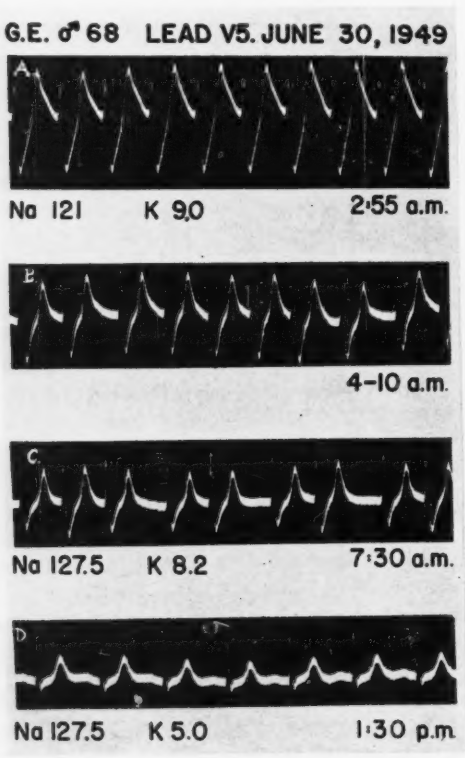

FIG. 6. Case 3. *A*. Bizarre complexes occurring at regular rhythm, rate 136, probably idioventricular rhythm. *B*. Tracing following glucose and insulin showing shortening of QRS complex and development of grossly irregular rhythm, probably auricular fibrillation. S-T still depressed, T waves still peaked. *C*. Further improvement following continued glucose-insulin therapy; rhythm still irregular. *D*. Normal curves with return of regular auricular activity following the artificial kidney.

Figure 6*B* was recorded after the patient received 50 Gm. of glucose and 25 units of insulin by vein. Two important developments were noted: the QRS shortened and the rhythm became grossly irregular. In other words, the mechanism seemed to improve in one regard and become worse in another. With further increments of glucose and insulin (total glucose 100 Gm., insulin 50 units) (fig. 6*C*) there was further improvement in the ventricular complexes (clearer delineation of the S-T segments, smaller T waves and a still shorter QRS interval) but the arrhythmia persisted. It was not until after hemodialysis that the electrocardiogram became normal with regular sinus rhythm (fig. 6*D*).

The observation that the electrocardiogram apparently became worse in one respect (the development of arrhythmia) while improving in another (shortening of the QRS complex) during therapy which decreases the degree of hyperkalemia, is of considerable interest. It suggests that the regression of the tissue changes associated with hyperkalemia may be spotty, some islands of myocardial tissue recovering their irritability before others. If this conception were valid the relative concentration of potassium in the auriculoventricular node and bundle, on the one hand, and in the ventricular pacemaker, on the other, might determine whether or not the latter might be "released." However, the fact that the ventricular complexes were of unchanging form is at some variance with the existence of an "escape" mechanism.

An explanation for this series of changes in rhythm, more consonant with current electrocardiographic teaching, would be that figure 6*A* represents idioventricular rhythm with either complete auricular asystole or auricular fibrillation* (fibrillation waves invisible) and that figure 6*B* represents either (1) the *return* of auricular fibrillation with irregular ventricular rhythm or (2) the *persistence* of auricular fibrillation with the subsidence of idioventricular rhythm and the resumption of some degree of auriculoventricular conduction*; and that figure 6*D* represents the return of sinoauricular rhythm.

Case. 4 Premature ventricular beats, auricular fibrillation: U waves during subsiding hyperkalemia. K. B., PBBH #5B46, a 35 year old housewife, was admitted to the hospital with a history of oliguria of eight days' duration which followed delivery of a child nine days before admission. In this case also, more detailed clinical, chemical and electrocardiographic data are presented in the parallel study[17]; in the present communication attention is focused

* This explanation has a pharmacologic parallel in digitalis intoxication. The inception of a regular idioventricular rhythm superimposed upon pre-existent and persistent auricular fibrillation is generally regarded as an advanced toxic effect of digitalis.

upon selected leads illustrating the disturbances of rhythm noted during the course of treatment of this patient. The initial tracings taken at 11:45 (fig. 7*A*) before treatment, showed typical changes of potassium intoxication. At this time the serum sodium level was 102 and the serum potassium 8.8 mEq. per L. and the patient was in coma. In lead the same form as the beats indigenous to this lead. From their resemblance to the usual complexes these beats must have arisen near the auriculoventricular node. The sixth complex was of the usual form for this lead and the seventh a premature ventricular beat. Premature ventricular beats, isolated or arranged in similar grouping, were in our

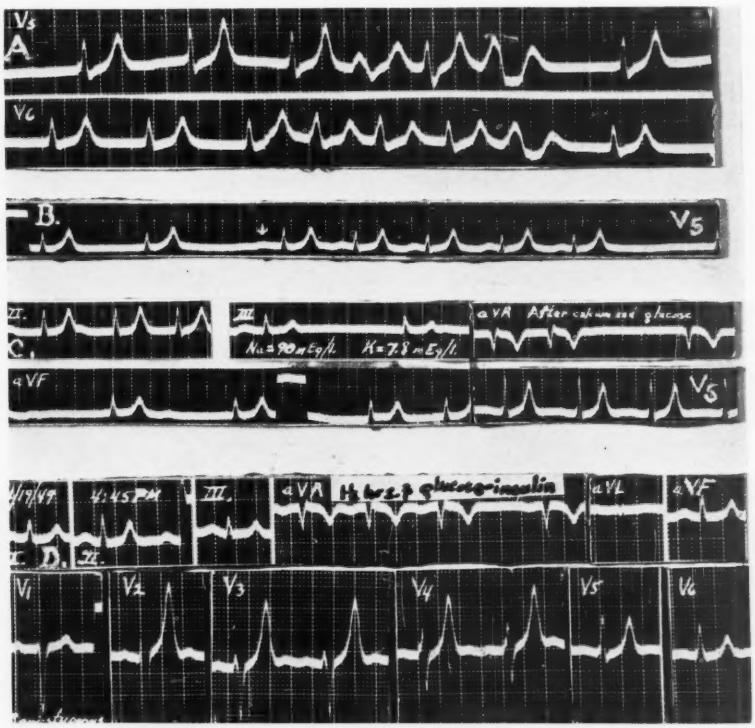

FIG. 7. Case 4. *A*. Short runs of ventricular premature beats in leads V_5 and V_6 in potassium intoxication. *B*. Tracings following sodium bicarbonate therapy showing alternating periods of (a) more rapid regular sinus rhythm, and (b) slow irregular rhythm associated with absence of P waves, probably auricular fibrillation. *C*. Following calcium therapy showing apparent alternation of sinus arrhythmia with auricular fibrillation. *D*. An hour and a half after glucose-insulin showing sharper P waves with sinus arrhythmia. Note appearance of U waves; serum potassium level at this time 7.3 mEq. per L.

V_5 auricular activity was not demonstrable. The dominant rhythm was slightly irregular; this was interrupted by a short run of rapid beats. The fourth and sixth complexes in this strip were ventricular premature beats. The intervening (fifth) beat was of the usual form seen in this lead but it showed some aberration. In lead V_6 taken immediately hereafter, another period of rapid heart action was recorded. This began with the third beat in the strip which was of approximately normal form showing a slight alteration, probably an artefact. The next two beats were premature and almost of experience recorded in only one other case of potassium intoxication.

Figure 7*B* taken of V_5 at 12:15, shortly after sodium bicarbonate therapy, when the sodium and potassium levels were 102 and 7.8 mEq. per L. respectively and the patient was becoming responsive, showed the return of normal intraventricular conduction and the sporadic reappearance of broad low P waves and a long P-R interval. When P waves were absent the rhythm was slower (about 36 beats to the minute) and slightly irregular; when P waves were present the rhythm was regular and about

twice as fast (72 beats to the minute). This might be explained as due to alternating periods of normal sinus rhythm and auricular standstill. If this were true, however, one would expect the ventricular pacemaker to beat at a regular rhythm during the period of auricular standstill. Since the ventricular rhythm was irregular it seems more reasonable that not yet recorded. It would be difficult to venture a precise definition of the arrhythmia present at this time but here again the most reasonable formulation would be alternation of auricular fibrillation and sinoauricular rhythm, occasionally arrhythmic. Sinus arrhythmia of the type described has been observed repeatedly in potassium intoxication. The same

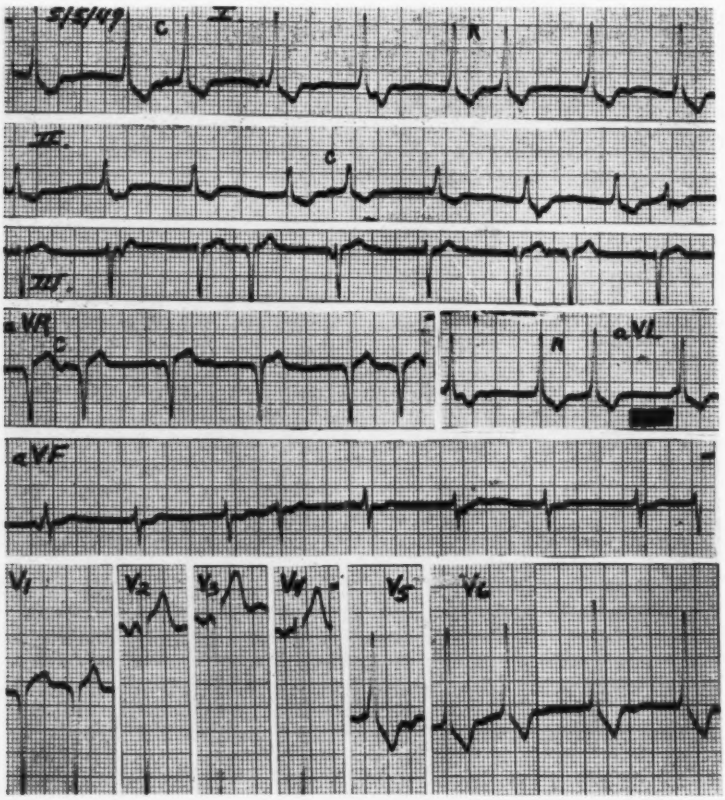

FIG. 8. Case 5. Electrocardiograms obtained from patient in congestive heart failure and probable pulmonary embolism when serum potassium was 5.8 and sodium 122 mEq. per L., showing interference and dissociation and characteristic changes of left ventricular enlargement. Auricular beats labelled *C* were conducted to the ventricles breaking up the idioventricular rhythm.

this strip represents alternation of auricular fibrillation with a slow ventricular rate and short periods of normal sinus rhythm.

Figure 7*C*, showing leads II, III, aV_R, aV_F and V_5, recorded at 1:15 following calcium therapy, showed sporadic, low voltage P waves. Except in the last lead illustrated, the auricular waves, when present, showed arrhythmia, apparently sinus arrhythmia. And the P-R interval, though prolonged, was variable. In lead V_5 consistent sinoauricular activity was present and the P-R interval quite fixed. Thus the auricular and ventricular rhythms were regular at 75 beats to the minute. U waves were

rhythm is illustrated also in figures 2 *B*, *C*, *G*, *H* and *I*. These observations suggest that either auricular fibrillation or sinus arrhythmia may account for the arrhythmias of supraventricular origin occurring during potassium intoxication. In other clinical conditions auricular fibrillation of recent onset is generally associated with coarse, easily recognizable fibrillation waves. Since such waves have not been recorded in cases of potassium intoxication reported as showing auricular fibrillation, the implicit or direct assumption has been made that in potassium intoxication fibrillation waves are not demonstrable. In view of the general decrease of all electrical activity

in the auricles in potassium intoxication, this assumption seems reasonable. This suggests that the experimental induction of auricular fibrillation in an animal previously rendered hyperkalemic might clarify this problem. That such a study would be difficult to evaluate is suggested by a related investigation carried out from a somewhat different point of view by Wiggers and co-workers.[13] These authors emphasized that ventricular fibrillation developing following the infusion of potassium salts is quite distinct from ventricular fibrillation induced by faradic stimulation.

Figure 7*D*, taken at 4:45, an hour and a half after glucose-insulin therapy, when the serum potassium level was 7.3 mEq. per L. revealed more clear-cut P waves but still showed a long P-R interval and sinus arrhythmia. This is most apparent in lead aV_R. In the precordial leads tall pointed T waves and, for the first time, well marked upright U waves were recorded, especially in leads taken over the right ventricle. U waves have been observed during the hypokalemia which may occur following diabetic acidosis.[19] We have observed U waves in about half of the tracings of patients with hyperkalemia and in most of those in whom the heart rate was slow enough to expose an interval between the T wave and the succeeding P wave or QRS complex adequate to permit the inscription of a U wave. In those cases with rapid rate, a U wave, though not visible, might have been obscured in the following P wave or QRS complex. Thus U waves may be present in hyperkalemia as well as hypokalemia and one cannot distinguish between these two extremes on the basis of the presence or absence of a U wave.

A subsequent tracing taken following the use of the artificial kidney was normal in every respect; U waves were still present.

Case 5. Interference and dissociation, left bundle branch block associated with hyperkalemia. H. H. V. PBBH #1B402, a 49 year old man with calcific aortic stenosis and insufficiency, angina pectoris, syncopal attacks and chronic congestive heart failure, was admitted on May 4, 1949 because of thrombophlebitis and pulmonary embolism. Electrocardiograms on the following day (fig. 8) showed interference and dissociation and characteristic changes of left ventricular enlargement. At this time the serum sodium level was 122 mEq. per L. and the serum potassium 5.8 mEq. per L. On the morning of May 7, the electrocardiogram (fig. 9) showed an irregular rhythm with broad P waves and changes very suggestive of potassium intoxication. In this instance, lead aV_L and additional leads in the posterior axillary line and the midscapular line at the same horizontal level as V_6 (i.e., leads $V_{7,8}$) showed late intrinsicoid deflections. This change, though not altogether characteristic, suggested the existence of left bundle branch block. The blood serum at this time contained 120 mEq. per L. of sodium and 6.9 mEq. per L. of potassium. The patient died later that morning in acute pulmonary edema. Permission for a postmortem examination was not obtained.

This is the first instance in the present series in which suggestive evidence of left bundle branch

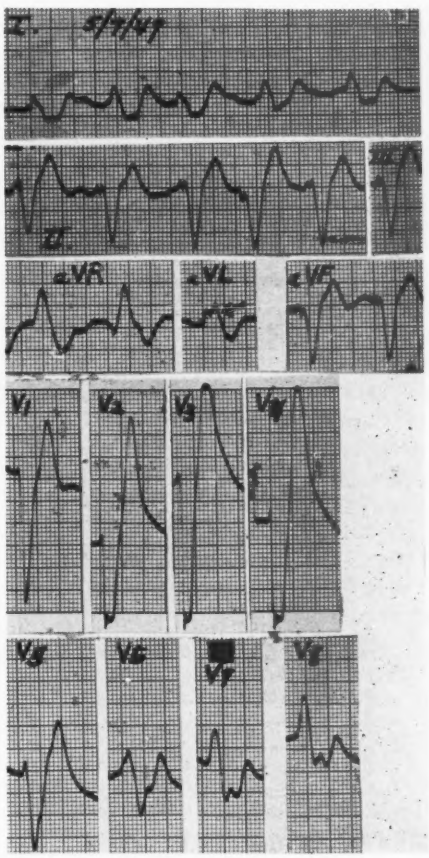

FIG. 9. Case 5. Tracings obtained three days later when patient was moribund and serum potassium 6.9 and sodium 120 mEq. per L. There is a bizarre arrhythmia with intraventricular block and sporadic auricular activity. A late intrinsicoid deflection was recorded in lead aV_L. Left bundle branch block is probable.

block was recorded, and the only case in which interference and dissociation was associated with hyperkalemia. The relationship between this chemical change and the electrocardiographic appearance is problematic. We wish merely to record their coexistence.

Case 6. The sequence of peaked T waves, left bundle branch block and diffuse intraventricular block in

hyperkalemia. P. P., PBBH #P2473, a 46 year old taxi driver with tabes dorsalis, diabetes and chronic nephritis was admitted on January 4, 1950 because of uremia. Throughout a long hospital stay he went steadily downhill, in spite of a great deal of elaborate therapy, and died on February 18, 1950. Postmortem examination showed left ventricular hypertrophy, coronary atherosclerosis without infarction and chronic passive congestion of the viscera. Microscopic examination of the kidneys showed chronic glomerulonephritis, chronic pyelonephritis and arteriolosclerosis. The initial set of electrocardiograms (fig. 10) taken during a previous admission were normal. The second set of tracings recorded shortly after the present admission showed tall pointed T waves, characteristic of hyperkalemia. At this time the serum potassium level was 6.6 mEq. per L. The third set of tracings, taken five days later, showed left left bundle branch block (QRS 0.13 second) with normal auriculoventricular conduction. The T waves were still tall and pointed, perhaps more so than one usually sees in uncomplicated left bundle branch block due to other causes. The final set of tracings taken one month later still showed left bundle branch block with peaked T waves but the QRS complex increased to 0.17 second and first degree auriculoventricular block was present (P-R interval 0.22 second). At this time the potassium level was the highest recorded in this patient (8.8 mEq. per L.). In subsequent tracings normal auriculoventricular conduction was present with left bundle branch block.

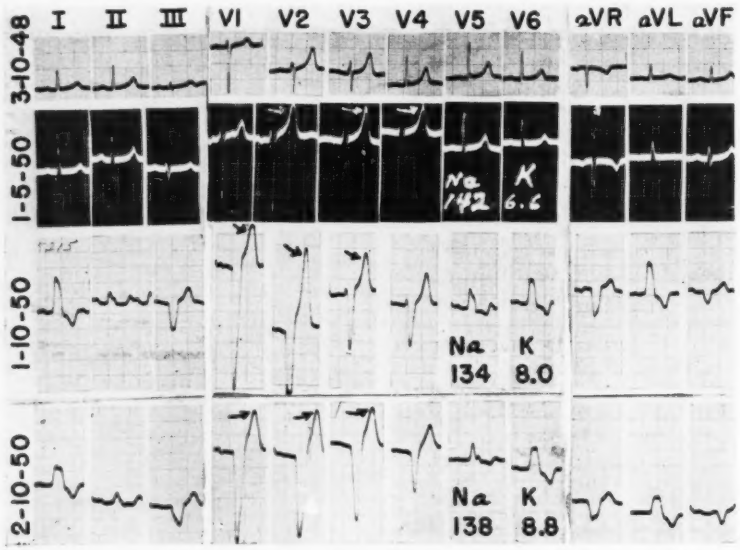

FIG. 10. Case 6. Normal initial set of tracings taken at the time of a previous admission for an infected finger. The second set, taken shortly after the final admission, shows tall, pointed T waves (see arrows) in leads V_2 through V_4. At this time the serum potassium level was 6.6 and the serum sodium 142 mEq. per L. The next two sets of tracings show left bundle branch block, apparently with superimposed peaked T waves. Numerous tracings obtained throughout his hospital stay resembled those recorded on January 10 but those obtained on February 10 showed first degree auriculoventricular block. (P-R interval 0.22 second) At this time the serum potassium level was 8.8, the serum sodium level 138 mEq. per L. The QRS interval increased from 0.13 second in the third set to 0.17 second in the final set of tracings, evidence of superimposed diffuse intraventricular block.

An impulse in a bundle branch may be delayed (incomplete bundle branch block) or blocked (complete bundle branch block). Once blocked it cannot suffer a greater degree of block. The further prolongation of the QRS interval in this case cannot therefore be attributed to "more" left bundle branch block. It is necessary then to attribute this change to diffuse intraventricular block involving the remainder of the ventricular myocardium. Yet the sequence of events recorded here should remind us that if the changes of diffuse intraventricular block develop very rapidly the transition through an intermediate stage of bundle branch block could be missed.

This was the first instance in the present series in which left bundle branch block was clearly demon-

strated. It is possible that bundle branch block was present in other cases but its features may have been swamped out in the general impairment of intraventricular conduction, or overlooked because of an inadequate number of leads. We felt, however, that our findings in these cases showing a prolonged QRS duration were more in line with those of Finch and co-workers[16] who considered that in potassium poisoning the defect in intraventricular conduction must be regarded as a more general one affecting the ventricle as a whole, myocardium proper and bundle branches alike.

Discussion

According to current teaching the surface of the cell, and more particularly of the myocardial cell, is polarized in the resting state, the charge upon the outer surface exceeding that on the inner surface. Among other factors, and perhaps most important of all, it is considered that the difference in potassium ion concentration between the outside and the inside of the membrane determines this difference in potential. If this normal differential is disturbed, as by painting a part of the surface of a nerve fiber, or of the epicardial surface of the entire heart, with potassium solution, that part of the nerve fiber or of the heart becomes partially or wholly incapable of responding to an electrical stimulus. The type of response is similar to that which develops if the same surface is injured mechanically, is cooled, or is deprived of its blood supply. It has been suggested that any of these procedures permits the migration of potassium ions from the inner to the outer surface of the cell, thus minimizing or eliminating the difference in potential across the cell membrane. By whatever means such a change has been produced, that portion of the surface which is less intensely polarized or which is no longer polarized, becomes less capable in the one case, or incapable in the latter, of responding to an electrical stimulus. Changes in the voltages of the deflections corresponding to depolarization and repolarization of the tissues in question are thereby produced. These considerations may explain the decrease in the voltage of the P wave and of the R wave observed in clinical potassium intoxication.

In addition to altering the magnitude of the electrical response of the heart muscle to the stimulating current in this way, potassium also slows the rate of conduction of the impulse in the myocardium. As a consequence, the P wave and the QRS complex are prolonged. Changes in the T wave could develop as "secondary" manifestations of the QRS changes or they might be "primary" and not accounted for on that basis. The prolongation of the Q-T interval characteristic of potassium intoxication could result from the prolongation of the QRS and/or T waves or from "primary" ischemic or ischemia-like changes. An evaluation of this problem by determination of the ventricular gradient in potassium poisoning is now in progress.

It has been shown[20-22] that solution of potassium salts applied to the epicardial surface of the heart produced a "current of injury" so that an electrode in relation to the surface bathed with potassium records upward deviation of the RS-T segment. This is similar to the change produced by searing the surface with the electric cautery or by producing ischemia or infarction of the same area by ligating the coronary artery nourishing this region. Conversely injury to the subendocardial layers of the myocardium similarly damaged[21] or injected with potassium solution[21, 22] produces, at an electrode in relation with the ventricular cavity, an elevation of the RS-T segment and a late deeply inverted T wave. At the same time an electrode in relation to the overlying epicardium records a ventricular complex the reverse of that just described, namely a depression of the RS-T segment,[21, 22] prolongation of the Q-T interval and a tall upright T wave.[23] The unipolar right arm lead (lead V_R or aV_R) being generally in relation with the ventricular cavities, ordinarily records a downward QRS complex, the composite effect of the endocardial potentials of the right and left ventricles. If potassium produces an effect similar to that of injury at the endocardial surface of the ventricles, one would expect that in potassium intoxication one would find, in association with the depressed S-T segments in the precordial leads, elevation of the S-T segments at the endocardial aspect of the ventricle and thus in lead aV_R as well. A review of all cases in this study shows that such changes are indeed recorded. In potassium poisoning then, multiple

lead electrocardiography shows that the heart behaves electrically as if it were the site of a predominantly subendocardial injury. If the subendocardial layers of the ventricle were more vulnerable than the muscle layers remote from the endocardium to the effect of the potassium-rich blood, then the existence of these changes might be explained. This view has been anticipated by Wiggers, Theisen and Shaw,[13] who felt that potassium produced depressed conduction first in the bundle branches and internal layers of the ventricle and subsequently in diverse portions of the myocardium. At the present time, however, this view must be regarded as possible but unproved.

In case 5 possible left bundle branch block was detected on the morning of the patient's death when the serum potassium level was 6.9 and the serum sodium level 120 mEq. per L. In case 6 clearcut left bundle branch block developed with the QRS duration lengthening from 0.13 to 0.17 second. Both of these patients showed sufficient prolongation of the QRS interval to demand the additional assumption of a profound degree of nonspecific intraventricular block. It is possible that if more extensive electrical exploration were made in all cases, more instances of bundle branch block would have been detected. The present observations are too limited to justify a statement as to whether a general delay in intraventricular conduction necessarily precedes the development of unmistakable evidences of bundle branch block or whether, as Wiggers and associates[13] maintained, and as seems more likely, the bundle branches and subendocardial tissues are the initial sites of block. In any event, it seems quite clear that in the more advanced stages of potassium intoxication with general delay in conduction and without the coordinating effect of specialized conducting tissue, the human heart behaves electrically like the lower vertebrate heart, which is made up of striated cardiac muscle but which lacks specialized conducting tissue,[24] or even like the smooth muscle heart of some of the lower invertebrates.[25]

It has been emphasized above that in view of the uncertainty as to whether auricular activity actually persists in the more severe grades of hyperkalemia, one frequently cannot differentiate between auricular fibrillation and sinus arrhythmia. When one is uncertain as to the type of auricular rhythm, the type of ventricular rhythm is equally uncertain. It is then impossible to say whether ventricular complexes are conducted from the auricles or arise independently as "idioventricular" beats. For this reason we have found it necessary to present alternative explanations of the rhythms in some of the cases described above. In the future such cases deserve study with the esophageal or intracardiac electrode.

Mechanism of Arrhythmias

It is impossible to venture a definite decision as to whether these arrhythmias develop as a result of myocardial depression with "escape" of nondepressed areas of the heart or as the result of increased irritability of certain parts of the heart. Cases of ventricular escape (case 1) and of premature ventricular beats (case 4) were encountered in the present study. The escape can reasonably be attributed to primary depression; the explanation for the latter depends upon the conception held of the mechanism of ventricular premature beats. There is as yet no agreement upon this point. If one considers these to be due to reentry or to emergence of impulses from a parasystolic focus, primary depression might be the primary mechanism: if due to heightened activity of an ectopic pacemaker or to the development of a supernormal phase or of a heightened supernormal phase, increased excitability might be the mechanism. We believe, however, that the weight of evidence in this study is in favor of the hypothesis that potassium intoxication produces these arrhythmias as result of its depressive action.

It is held by some authorities that abnormal rhythms arising in the course of acute myocardial infarction may be "triggered" by local "currents of injury" dependent upon differences in the degree of polarization of contiguous areas of the myocardium. Similar local differences in the degree of potassium depression of the myocardium have been postulated. It is conceivable that such differences in the potential change across the cell membrane may initiate the abnormal normotopic and heterotopic rhythms

which may develop in the course of potassium intoxication. It is even possible, in fact, that the abnormality in either condition involves a similar mechanism, namely local differences in surface ion (and particularly potassium ion) distribution. The relationship between these disturbances of impulse *formation* and impulse *conduction* is unknown: it seems reasonable, however, that some relationship must exist between the two.

Effect of Potassium through Anoxia and Nervous Influences

Potassium intoxication probably influences the heart and the electrocardiogram not merely through its direct myocardial effect but also through other, more complicated, and as yet even more vaguely understood mechanisms. Thus, impaired contractility of the heart may be associated with decrease in coronary perfusion and result in myocardial anoxia.[26] This anoxia, acting directly or through changes in electrolytes in the myocardium,[27] may be capable of producing profound electrocardiographic effects. Furthermore, there is evidence that nervous influences mediated through the sympathetic and parasympathetic divisions of the autonomic nervous sytem influence the development of abnormal cardiac rhythms. Increased vagal tone or sympathicomimetic drugs can predispose to or actually induce auricular fibrillation.[28] Although the idea has been abandoned that potassium is actually the chemical agent causing ganglionic discharge at parasympathetic nerve endings, there is some evidence that movement of potassium ions may in some way be concerned with the release of acetylcholine.[29] Potassium is also capable of stimulating sympathetic ganglions and initiating epinephrine discharge.[30] Although epinephrine itself is probably not a fibrillatory drug[31] it may under certain circumstances, such as light chloroform anesthesia,[22, 32] act in this way. It is apparent then that the influence of potassium upon the heart is a complicated one and depends, among other factors, upon myocardial anoxia and upon its effects on vagal and accelerator mechanisms as well as upon its direct action on heart muscle.

Potassium and "Cor Mortem"

One of the first two cases[34] of potassium intoxication reported from this clinic was found in retrospect by a review of the "cor mortem" tracings in the electrocardiographic file. From a review of the literature and their own experience Stroud and Feil[35] recently constructed the following composite summary of the terminal electrocardiographic sequence in individuals who did not die suddenly; "The initially rapid rate with sinus rhythm slows . . . There is prolongation of the auriculo-ventricular conduction time. Then excitation is initiated in the auriculo-ventricular node. Next auricular activity ceases as the ventricular pacemaker develops. At this time if many ectopic foci become active ventricular flutter and fibrillation may ensue. Then, either the rate slows and the heart stops, or the rate increases and again a flutter-fibrillation may occur . . . The QRS complex widens and is reduced in amplitude. The T waves become larger and, if inverted, become upright. Finally the QRS and T merge into a monophasic positive wave . . . " It is apparent at once that this is an apt description of the terminal sequences in experimental and clinical potassium intoxication. Although studies of blood potassium were not made, it is quite probable that in many of these terminal tracings published in the medical literature (for example, Stroud and Feil's second case, one of carbon tetrachloride poisoning and uremia), potassium intoxication was the actual cause of the terminal rhythm. Although anoxia is probably of primary importance, we do not yet know whether similar mechanisms developing terminally in coronary artery disease or acute myocardial infarction are implemented, in one way or another, by alterations of extra- and/or intracellular potassium in the heart muscle.

The recent demonstration[36] of variation in the height of the T wave in association with changes within what is generally considered the normal range of potassium concentration is of considerable interest. These findings may explain some of the normal variations in the T wave as well as the extreme difficulty we have experienced in trying to decide whether the tall or suggestively peaked T waves seen in a

given tracing fall within or beyond the normal range.

Summary

Many cases of potassium intoxication develop a grossly irregular slow ventricular rhythm. At times this is associated with persistent but feeble electrical activity in the auricles and must be attributed to sinus arrhythmia. At other times electrical activity cannot be demonstrated in the auricles; it is believed that auricular fibrillation may exist in these cases. With increasing severity of potassium intoxication the rhythm may again become regular; this can be explained by the development of idioventricular (nodal) rhythm. In one patient interference and dissociation was recorded when the serum potassium level was elevated. In most cases hyperkalemia was associated with a diffuse slowing of intraventricular conduction; in one patient probable, and in another definite, left bundle branch block was demonstrated. First degree auriculoventricular block was commonly encountered but higher grades of auriculoventricular block could not be recognized because of disappearance of the P waves. U waves are commonly present in hyperkalemia.

Ectopic ventricular complexes occurring either as escape or premature beats were recorded singly or in paroxysms. The electrocardiographic appearance of "ventricular flutter" recorded in one patient with potassium intoxication changed to that characteristic of ventricular tachycardia during glucose-insulin therapy and before the tracings, on continuation of the same therapy, reverted to a more normal appearance. This patient later died of ventricular fibrillation. It is not known whether these ectopic rhythms develop as a result of increased or decreased myocardial excitability, though the data in this study seem more compatible with the latter view. In hyperkalemia the heart behaves electrically (elevated S-T in lead aV_R; depressed S-T in the precordial and in some of the limb leads) as if the potassium-rich blood exerts a greater "injury" effect upon the subendocardial fibers than is exerted elsewhere in the heart.

Acknowledgment

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References

1 Winkler, W. W., Hoff, H. E., and Smith, P. K.: Cardiovascular effects of potassium, calcium, magnesium and barium. Yale J. Biol. & Chem. **1** . 123, 1940–41.

2 Fenn, W. O.: The role of potassium in physiological processes. Physiol. Rev. **20:** 377, 1940.

3 Mathison, G. C.: The effects of potassium salts upon the circulation and their action on plain muscle. J. Physiol. **42:** 471, 1911.

4 Nahum, L. H., and Hoff, H. E.: Observations on potassium fibrillation. J. Pharmacol. & Exper. Therap. **65:** 322, 1939.

5 McLean, F. C., Bay, E. B., and Hastings, A. B.: Electrical changes in the isolated heart of the rabbit following changes in the potassium content of the perfusing fluid. Am. J. Physiol. **105:** 72, 1933.

6 Chamberlain, F. L., Scudder, J., and Zwemar, R. L.: Electrocardiographic changes associated with experimental alterations in blood potassium in cats. Am. Heart J. **18:** 458, 1939.

7 Hering, H. E.: Über erregende Wirkungen der Kalium auf das Säugertierherz (extrasystolische Tachykardie, Flimmern). Pflüger's Arch. f. d. ges. Physiol. **161:** 544, 1915.

8 Nicholson, W. M., and Soffer, L. J.: Cardiac arrhythmias in experimental suprarenal insufficiency in dogs. Bull. Johns Hopkins Hosp. **56:** 236, 1935.

9 —, and Schechter, A. J.: Cardiac arrhythmias after bilateral ureteral ligation in the dog. Bull. Johns Hopkins Hosp. **60:** 346, 1937.

10 Winkler, A. W., Hoff, H. E., and Smith, P. K.: Electrocardiographic changes and concentration of potassium in serum following intravenous injection of potassium chloride. Am. J. Physiol. **124:** 478, 1938.

11 Keith, N. M., and Burchell, H. B.: Clinical intoxication with potassium: its occurrence in severe renal insufficiency. Am. J. M. Sc. **217:** 1, 1949.

12 MacWilliam, J. A.: The mechanism and control of fibrillation in the mammalian ventricle. Proc. Roy. Soc., London, s. B. **90:** 302, 1917–19.

13 Wiggers, C. J., Theisen, H., and Shaw, H. D. B.: Studies on ventricular fibrillation produced by electric shock. III. The action of antagonistic salts. Am. J. Physiol. **93:** 197, 1930.

14 Crismon, J. M., Crismon, C. S., Calabrese, M., and Darrow, D. C.: Electrolyte redistribution in cat heart and skeletal muscle in potassium poisoning. Am. J. Physiol. **139:** 667, 1943.

15 Wilson, F. N., Johnston, F. D., Rosenbaum,

F. F., Erlanger, H., Kossman, C. E., Hecht, H., Cotrim, N., de Oliveira, R. M., Scarsi, R., and Barker, P. S.: The precordial electrocardiogram. Am. Heart J. **27:** 19, 1944.

[16] Finch, C. A., Sawyer, C. G., and Flynn, J. M.: Clinical syndrome of potassium intoxication. Am. J. Med. **1:** 337, 1946.

[17] Merrill, J. P., Levine, H. D., Somerville, W., and Smith, S., III.: The clinical recognition and treatment of potassium intoxication. Ann. Int. Med. **33:** 797, 1950.

[18] Wilson, F. N., and Herrmann, G. R.: Some unusual disturbance of the mechanism of the heart beat. II. Toxic depression of the conductivity of the Purkinje system. Arch. Int. Med. **31:** 923, 1923.

[19] Nadler, C. S., Bellet, S., and Lanning, M.: Influence of the serum potassium and other electrolytes on the electrocardiogram in diabetic acidosis. Am. J. Med. **5:** 838, 1948.

[20] Wiggers, C. J.: Monophasic and deformed ventricular complexes resulting from the surface application of potassium salts. Am. Heart J. **5:** 346, 1929–30.

[21] Wolferth, C. C., Bellet, S., Livezey, M. M., and Murphy, F. D.: Negative displacement of the RS-T segment in the electrocardiogram and its relationship to positive displacement; an experimental study. Am. Heart J. **29:** 220, 1945.

[22] Hellerstein, H. K., and Katz, L. N.: The electrical effects of injury at various myocardial locations. Am. Heart J. **36:** 184, 1948.

[23] Byer, E., Ashman, R., and Toth, L. A.: Electrocardiograms with large upright T waves and long Q-T intervals. Am. Heart J. **33:** 796, 1947.

[24] Clark, A. J.: Comparative Physiology of the Heart. London, Cambridge University Press, 1927.

[25] Evans, C. L.: Vergleichend-toxikologische Spezifität des chemischen Alterationsstromes, zugleich ein Beitrag zur vergleichende Physiologie und Toxikologie des Herzens der Helix pomatia (snail heart). Ztschr. f. Biol. **59:** 397, 1912–13.

[26] Katz, L. N., and Lindner, E.: The action of excess sodium, calcium and potassium on the coronary vessels. Am. J. Physiol. **124:** 155, 1938.

[27] Dennis, J., and Moore, R. M.: Potassium changes in the functioning heart under conditions of ischemia and of congestion. Am. J. Physiol. **123:** 443, 1938.

[28] Altschule, M. D.: Relation between vagal activity and auricular fibrillation in various clinical conditions. New England J. Med. **233:** 265, 1945.

[29] Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics. New York, The Macmillan Company, 1941. P. 597.

[30] Knoefel, P. K., and Alles, G. A.: Physiological actions of potassium and epinephrin. J. Pharmacol & Exper. Therap. **63:** 17, 1938.

[31] DiPalma, J. R., and Schultz, J. E.: Antifibrillatory drugs. Medicine **29:** 123, 1950.

[32] Levy, A. G.: The exciting causes of ventricular fibrillation in animals under chloroform anaesthesia. Heart **4:** 319, 1912–13.

[33] Hill, I. G. W.: Cardiac irregularities during chloroform anaesthesia. Lancet **1:** 1139, 1932.

[34] Finch, C. A., and Marchand, J. F.: Cardiac arrest by the action of potassium. Am. J. M. Sc. **206:** 507, 1943.

[35] Stroud, M. W., and Feil, H. S.: The terminal electrocardiogram; twenty-three case reports and a review of the literature. Am. Heart J. **35:** 910, 1948.

[36] Schlachman, M., and Rosenberg, B.: The effect of potassium on inverted T waves in organic heart disease. Am. Heart J. **40:** 81, 1950.

Anatomic and Electrocardiographic Position of the Heart

By NOBLE O. FOWLER, M.D., AND JOHN R. BRAUNSTEIN, M.D.

Thirty-four patients were studied by electrocardiogram for electrical position of the heart, and by x-ray and angiocardiogram for anatomic position of the heart. A significant association between electrocardiographic and anatomic positions of the heart was found insofar as rotation about the anteroposterior and longitudinal axes is concerned. No association between electrocardiographic and anatomic positions was found with regard to rotation about the transverse axis.

THE HEART may rotate about three anatomic axes: anteroposterior, becoming horizontal or vertical in position; longitudinal, becoming clockwise or counterclockwise in position as viewed from the apex; and transverse, causing the apex to move forward or backward. This is illustrated in figures 1, 2, and 3. This study was undertaken in order to ascertain whether or not the rotation of the heart about its three axes can be estimated from ordinary unipolar electrocardiographic leads.

In 1942, Master[1] presented a detailed study concerning the effect of change in heart position upon the configuration of the standard leads of the electrocardiogram. In the same year Wilson[2] described six positions of the heart from the electrocardiographic standpoint: horizontal, semihorizontal, vertical, semivertical, intermediate, and indeterminate. These positions were determined from a study of the relationship between the unipolar extremity leads and the unipolar precordial leads, and were concerned with rotation around the anteroposterior axis only. In 1943, Gardberg and Ashman,[3] and in 1946, Ashman[4] described forty-five electrocardiographic positions of the heart in the three standard leads produced by rotation of the heart about three axes: anteroposterior, transverse, and longitudinal. In the most recent edition of his monograph, Goldberger[5] described criteria for determining the position of the heart with rotation about its three axes, using the unipolar extremity and precordial leads.

However, there have been few studies of the correlation between the electrocardiographic and anatomic positions of the heart in man. In 1946, Hyman, Failey, and Ashman[6] showed that rotation of the human heart about its anteroposterior axis could be satisfactorily predicted from the standard electrocardiographic leads, using the criteria described by Ashman.[4] In 1950 Rosenman and Katz[7] indicated that studies in their laboratory had shown a high degree of correlation between the configuration of the unipolar electrocardiographic leads and the anatomic rotation of the heart about its anteroposterior axis if the heart were not grossly enlarged. There has been, however, no study to indicate whether or not rotation of the heart about its transverse and longitudinal axes can be determined from the electrocardiogram. For this reason the following study was made.

Material and Methods

Thirty-four subjects, selected from the wards of the Cincinnati General Hospital, were studied. Those having electrocardiograms which showed clearly the electrocardiographic position of the heart were given preference.

Anatomic Axes

Rotation about Anteroposterior Axis. A 7 foot anteroposterior teleroentgenogram of the chest was taken with the subject in the supine position. On the developed film, a line was drawn from the cardiac apex to the junction of the lower border of the right pulmonary artery with the cardiac silhouette. The

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angle between this line and the horizontal of the roentgenogram was measured. This angle was used to determine the degree of rotation about the anteroposterior axis, a small angle indicating a horizontal position of the heart and a large angle, a vertical position of the heart.

Rotation about Transverse Axis. A 7 foot left lateral teleroentgenogram of the chest was made with the subject in the supine position. On the developed film, a line was drawn from the cardiac apex to the center of the lower border of the hilum of the lung. The angle between this line and the horizontal of the subject was measured. This angle was used to indicate the degree of forward or backward movement of the cardiac apex: a small angle indicated a backward displacement of the apex and a large angle, a forward displacement of the apex.

Rotation about Longitudinal Axis. With the subject in the supine position, an angiocardiogram was made according to the technic of Robb and Steinberg.[3] Films were taken with the x-ray tube at a distance of 5 feet, the maximum permitted by the machine. After the injection of a radiopaque dye, films were exposed every half-second, using a Fairchild camera. Upon the developed films, the location of the junction between right and left ventricles was noted as shown by the dye-filled right ventricle. Since anterior or ventral rotation of the right ventricle occurs in clockwise rotation, and anterior rotation of the left ventricle in counterclockwise rotation,[5] the degree of clockwise and counterclockwise rotation about the longitudinal axis could be determined. The per cent of the transverse diameter of the heart occupied by the right atrium and right ventricle at the level of the apex was measured. The distance from the midsternal line of the body to the left border of the right ventricle was also measured.

Electrocardiographic Position.

With the subject supine, the electrocardiogram was made with the Cambridge Simplitrol Electrocardiograph immediately before or immediately after the taking of the x-rays and angiocardiogram. Three standard leads, three unipolar extremity leads, and six or more unipolar precordial leads were taken. The criteria of electrocardiographic position outlined by Goldberger[5] were used.

Anteroposterior Axis. The heart was considered to be horizontal if lead a V_L contained a qR* or QR complex. The heart was considered vertical if lead aV_L contained QS or rS pattern.

Transverse Axis. The apex was considered to be displaced forward if lead aV_L contained a qR complex. The apex was considered displaced backward if lead aV_F contained an rS complex or RS pattern.

Longitudinal Axis. Clockwise rotation was considered to be present if lead aV_F contained a qR, QR, rS or RS complex. Counterclockwise rotation was considered to be present if leads V_2, V_3, or V_4 contained a qR complex.

* Following the usual convention, a small letter is used to indicate a relatively small deflection; a capital letter is used to indicate a relatively large deflection.

Results

Anteroposterior Axis. The departure from the horizontal, as measured by x-ray, ranged between 22 and 54 degrees. For the purpose of statistical analysis, patients having rotation between 22 and 37.9 degrees were considered to have horizontal hearts. Those having rotation between 38 and 54 degrees were considered to have vertical hearts. Twenty-six of the 34 cases studied had electrocardiograms showing either horizontal or vertical position of the heart. Eighteen of these cases had normal electrocardiograms. The results are shown in table 1. In only 3 cases did the electrocardiographic and anatomic positions fail to agree; only one of these was in a patient having a normal

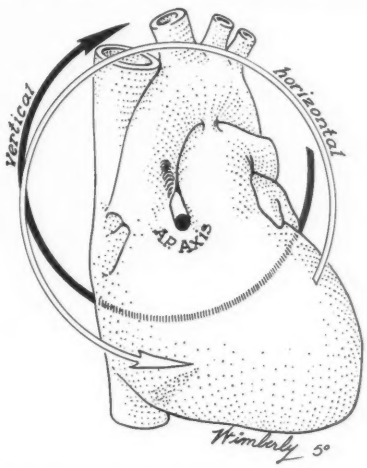

FIG. 1. Diagram of rotation of the heart about its anteroposterior axis.

TABLE 1.—*Rotation of the Heart about Its Anteroposterior Axis*

Electrocardiographic Position	Anatomic Position	
	No. Vertical	No. Horizontal
No. Vertical	11	0
No. Horizontal	3	12
$X^2 = 11.65$; $p < 0.01$		

electrocardiogram. In the 3 cases where the x-ray and electrocardiogram failed to agree, the hearts were vertical anatomically and horizontal electrocardiographically. In each of these 3 cases the hearts were only slightly vertical, having anatomic axes at 40, 40 and 41 degrees from the horizontal. The results shown in table 1 were analyzed by the chi square test and were found to show a high degree of association between the anatomic and electrocardiographic positions insofar as rotation about the anteroposterior axis is concerned. Chi square was 11.65, giving a p much less than 0.01, which is a highly significant value, and would occur by chance much less often than once in one hundred times.

TABLE 2.—*Rotation of the Heart about Its Transverse Axis*

Electrocardiographic Position	Anatomic Position	
	No. Forward	No. Back
No. Forward	6	7
No. Back	8	6
$X^2 = 0.495$; $p > 0.50$		

Transverse Axis. The angles found after mensuration upon the films varied from 25 to 57 degrees. Those hearts having an angle between 25 and 40.9 degrees were considered to have backward rotation of the apex; those having angles between 41 and 57 degrees were considered to have forward rotation of the apex. Twenty-seven of the 34 cases studied had electrocardiograms showing forward or backward rotation of the cardiac apex in accordance with the criteria given above. Eighteen of the 34 cases studied had normal electrocardiograms. The results are shown in table 2. In only 12 of the 27 cases did the electrocardiographic and anatomic positions agree. A statistical analysis of the results, using the chi square test gave a p value of slightly more than 0.50, indicating no statistical significance in the results obtained. In other words, in 12 cases out of 27, electrocardiographic position could easily be the same as the anatomic position as a result of chance alone.

Longitudinal Axis. Angiocardiograms were made in 22 of the 34 patients. Those cases in whom the right atrium and right ventricle occupied 26.6 per cent to 47.4 per cent of the transverse diameter of the heart were considered to have counterclockwise rotation; those in whom the right auricle and right ventricle occupied 47.4 per cent to 68.3 per

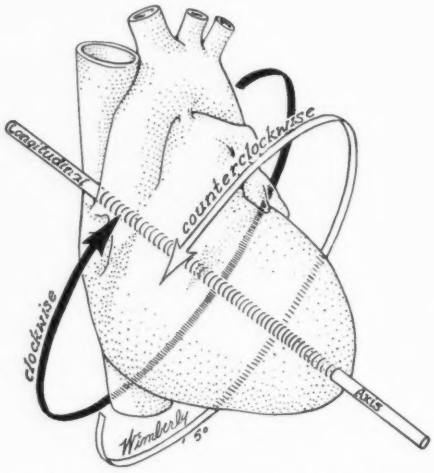

FIG. 2. Diagram of rotation of the heart about its longitudinal axis.

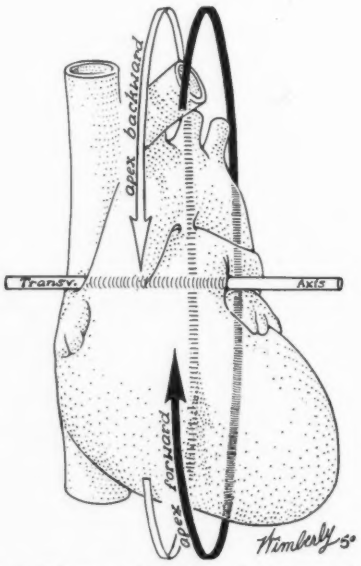

FIG. 3. Diagram of rotation of the heart about its transverse axis.

cent of the transverse diameter of the heart were considered to have clockwise rotation about the longitudinal axis. Unfortunately, only 13 of the 22 cases studied had electrocardiograms revealing definite clockwise or counterclockwise rotation according to the criteria above. The results are shown in table 3. The number of cases is too small to be analyzed by the chi square test. In order to study the problem in another way, a graph of the electrocardiographic and anatomic locations of the transitional zones was made (fig. 4). The ordinate shows distances from the midline of the chest to the left border of the right ventricle. The abscissa shows the location of the transitional zone according to the precordial unipolar leads of the electrocardiogram. The transitional zone electrocardiographically is taken at the point where the R and S waves of one of the six unipolar precordial leads were of equal amplitude. As shown by the graph, the correlation is by no means linear. However the correlation coefficient was calculated. The r value was 0.63. This value is very significant since any r above 0.590 is significant at the 1 per cent level when there are sixteen degrees of freedom and two variables, as in the present instance. It also indicates that there is a very significant correlation between the anatomic and electrocardiographic locations of the transitional zone. Both, however, are influenced by other factors and one can by no means be predicted from the other with any degree of accuracy.

TABLE 3.—*Rotation of the Heart about Its Longitudinal Axis*

Electrocardiographic Position	Anatomic Position	
	No. Clockwise	No. Counterclockwise
No. Clockwise	7	2
No. Counterclockwise	4	0
Undetermined	5	3

DISCUSSION

Wilson,[2] in discussing rotation about the anteroposterior axis, indicated that there should exist a high degree of correlation between electrocardiographic and anatomic positions of the heart, but stated that perfect correlation should not be expected. The best correlation, according to Wilson,[2] is to be anticipated when the electrocardiogram is normal, or shows no abnormality other than ventricular hypertrophy or bundle branch block. The high degree of correlation found in this study between electrocardiographic and anatomic positions of the heart with regard to rotation about the anteroposterior axis bears out Wilson's statement.

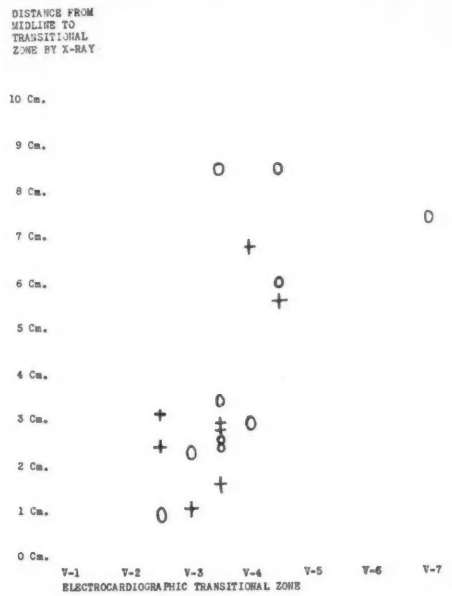

FIG. 4. Correlation of anatomic and electrocardiographic transitional zones.

The lack of significant association between electrocardiographic and anatomic position of the heart insofar as rotation about the transverse axis is concerned would seem to indicate that the electrocardiographic criteria of Goldberger cannot be used to predict rotation about the transverse axis. Goldberger[5] admits that in horizontal hearts, the apex may be backward by his criterion—that is, lead aV_F shows an rs or RS pattern—and forward when seen fluoroscopically.

Unfortunately, insufficient cases were studied to test the criteria of Goldberger with regard to electrocardiographic prediction of rotation

of the heart about the longitudinal axis. However, the validity of the location of the electrocardiographic transitional zone as a criterion of rotation about the longitudinal axis was tested. A significant correlation was shown between the electrocardiographic and anatomic locations of the transitional zones. The correlation between the two is not linear, however, and it must be borne in mind that backward displacement of the apex may cause an apparent shift of the transitional zone to the left in the electrocardiogram.

Summary and Conclusions

An electrocardiographic and anatomic study of rotation of the heart about its anteroposterior, transverse, and longitudinal axes was made in 34 subjects. A high degree of correlation was found between the electrocardiogram and x-ray insofar as rotation about the anteroposterior axis is concerned. No correlation between the electrocardiogram and x-ray was found with regard to rotation about the transverse axis. With regard to rotation about the longitudinal axis, there was found a very significant correlation between electrocardiographic and roentgenologic locations of the transitional zone.

Acknowledgments

The writers wish to thank Dr. Benjamin Felson of the X-Ray Department of the Cincinnati General Hospital for his assistance in obtaining the angiocardiograms, and Miss Mary Maciel of the Department of Surgical Art of the Cincinnati General Hospital for the drawings of the heart.

References

[1] Master, A. M.: The Electrocardiogram and X-Ray Configuration of the Heart, ed. 2. Philadelphia, Lea and Febiger, 1942.

[2] Wilson, F. N., Johnston, F. D., Rosenbaum, F. F., Erlanger, H., Kossmann, C. E., Hecht, H., Cotrim, N., Menzes de Oliveira, R., Scarsi, R., and Barker, P. S.: The precordial electrocardiogram. Am. Heart J. **27:** 19, 1944.

[3] Gardberg, M., and Ashman, R.: The QRS complex of the electrocardiogram. Arch. Int. Med. **72:** 210, 1943.

[4] Ashman, R.: Estimation of heart position from the QRS complex. Archivos del Instituto de Cardiología de México. **16:** 139, 1946.

[5] Goldberger, E.: Unipolar Lead Electrocardiography, ed. 2. Philadelphia, Lea and Febiger, 1949.

[6] Hyman, A., Failey, R. B., and Ashman, R.: Can the longitudinal anatomical axis of the ventricles be estimated from the electrocardiogram? Am. Heart J. **36:** 906, 1948.

[7] Rosenman, R. H., and Katz, L. N.: The role of multiple V chest and aV limb leads in routine clinical electrocardiography. Mod. Concepts Cardiovasc. Dis. **19:** 65, 1950.

[8] Robb, G. P., and Steinberg, I.: Visualization of the chambers of the heart, the pulmonary circulation, and the great blood vessels in man: a practical method. Am. J. Roentgenol. **61:** 1, 1939.

Unipolar Bronchial Electrocardiographic Exploration of the Heart in Man

A Preliminary Report*

By Isac Goldstein, M.D., Leon Pordy, M.D., Kenneth Chesky, M.D., Harold S. Arai, M.D., Eugene R. Snyder, M.D., and Sidney Feuerstein, M.D.

The method for exploring cardiac potentials through the bronchial tree is described in detail. It consists of obtaining unipolar bronchial leads by inserting a thin No. 4 French catheter into the secondary branches of the bronchial tree as near as possible to the surface of the heart. By this method, electrocardiograms can be obtained on the right side which resemble right auricular endocardiograms. On the left side, left ventricular epicardial and cavity potentials are recorded and these are similar to direct left ventricular surface leads, left intraventricular cavity potentials and esophageal leads at the same level. No arrhythmias or serious reactions occurred during or after this procedure. Preliminary findings in 8 cases are discussed in detail.

THE STANDARD limb leads have been supplemented in the past 20 years by leads with exploring electrodes placed near the heart. These supplementary leads did not include bronchial exploration because the lung was considered the poorest conductor of electricity in the body.[1–3] The first successful attempt to approach close to the heart in man, reported in 1906 by Cremer,[4] with an electrode in the esophagus, was reapplied by Lieberson and Liberson[5] and then by Brown in 1936.[6, 7] After the fundamental work on left ventricular surface leads in dogs by Lewis and Rothschild[8] in 1915, it became apparent that the heart should be approached in man even more directly. Einthoven himself utilized electrodes placed upon the chest. Ackerman,[9] then Wolferth and Wood,[10] and Wilson and his associates[11a, b] firmly demonstrated the diagnostic value of the precordial leads. Following the first venous right heart catheterization in 1929 by Forssmann on himself for pressure readings,[12] 16 years elapsed before Lenègre and Maurice[13] employed this method in man for intracavity electrocardiograms. This was followed by important contributions in this field by others.[14–21] Left cavity potentials in man have been obtained by the difficult procedure of left heart catheterization by other workers.[17, 23, 43] Direct epicardial electrocardiograms were taken by different investigators during thoracic exploration.[22, 44] In animal experiments, extensive studies using direct endo-epicardial leads have been performed in the past 10 years.[24, 26]

The information obtained by venous catheterization is usually limited to the right heart and that from esophageal exploration is restricted to potentials similar to those of the left auricular and ventricular cavities and the posterior surface of the left ventricle. Since the left ventricle in man is the most important seat of coronary disease, we were interested in finding a practical method for exploring the left ventricle closer to its surface than the customary precordial leads. The method of direct cardiac surface leads of Groedel and Borchardt[27] is obviously not a practical method for routine clinical investigation.

The senior author (I. G.) proposed the method for obtaining unipolar electrocardiograms by inserting an exploring electrode through the bronchial tree in order to be as near the heart as possible. The primary purpose of this procedure was to explore the left ventricular surface extensively by a clinically feasible method.

Later, extensive search of the literature revealed that Savjaloff,[28a, b] a Bulgarian physiologist, performed experiments in 1928 and 1929 to test the validity of the Einthoven triangle theory in the horizontal plane; he recorded bipolar leads after inserting a wire in each of the lower

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bronchi of a laryngectomized patient. Savjaloff also suggested the application of the method to patients with normal airways, by inserting the wires during bronchoscopy: he stated that this method was superior to standard electrocardiography for the study of P waves. No further work was performed along this line by others because of the accepted idea that the lung is a poor electrical conductor. The procedure of Savjaloff differs from the method of unipolar bronchial electrocardiographic exploration in that the latter provides a safe, relatively simple method for obtaining unipolar potentials similar to those from the right cavities (as in right heart catheterization), from the left heart cavities (as in esophageal leads at corresponding levels and in left heart catheterization), and finally from the surface of the left ventricle. The latter represents the most important contribution of this method.

However, at the completion of our preliminary studies, Langner and Atkins[29] independently published their observations in 10 individuals with the method of intrabronchial electrocardiography. They reported analysis only of the contours of the QRS complexes with the intrabronchial leads and concluded that potential variation distribution in the lungs corresponded approximately and qualitatively with the potential variation distribution recorded from the surface of the body.

Methods

The procedure of bronchial electrocardiographic exploration was performed in a preliminary group of 8 subjects. They were divided into two groups: (1) 3 with laryngectomies and tracheal fistulas and (2) 5 with normal airways (first to one of us—I.G.). We employed an insulated wire (in a No. 4 French ureteral catheter), 45 cm. in length, and with a rounded German silver tip. This was used as the unipolar exploring electrode (V), and the central terminal of Wilson was utilized as the reference electrode.*

The patients were examined in the fasting state and, when indicated, mild barbiturate sedation was administered (45 to 90 mg. Seconal by mouth). Electrocardiograms were taken routinely both in the recumbent and standing positions and these included the three standard limb, the three unipolar extremity, and complete circumferential unipolar (V) chest leads—a total of twenty-two leads. This procedure was followed by routine fluoroscopy of the chest.

An otolaryngologist (E. R. S. or S. F.) assisted in the insertion and positioning of the bronchial electrode. In the cases with tracheal fistulas, satisfactory local anesthesia for over one-half hour was obtained with 1 cc. of a 20 per cent cocaine hydrochloride solution sprayed through the fistula into the trachea. The exploring electrode was inserted directly and easily. In the other patients, anesthesia of the pharynx and upper larnyx was obtained first by similar spray with cocaine solution and then the tracheobronchial tree was anesthetized by aerosolization of the cocaine solution. The catheter was then inserted via the normal pathway in these cases.

The patients were explored either in the standing or recumbent position. Under direct fluoroscopic control, the catheter was moved into various positions in the bronchial tree. During changes of catheter position, some patients experienced cough with expectoration of mucus which was easily controlled through aspiration. When technical conditions permitted, spot films were taken of the catheter in both posterior-anterior and oblique positions for accurate determination of the position of the catheter in relation to the heart.

The technic employed was introduction of the catheter first on the right side. This was performed easily because of the anatomic relations. Leads are taken preferably during quiet respiration. The first lead (RBa-1) is taken with the catheter tip located in an anterior secondary branch of the right lower bronchus at the level of the right leaf of the diaphragm and as near and anterior to the heart as possible. Positions RBm-1 and RBp-1 are located in the middle and posterior branches of the right lower bronchus at the same level (fig. 6). By withdrawing the catheter tip cephalad to the level of the right supracardiac junction, the second position is determined (RB-2: main stem of the right lower bronchus at the level of the right supracardiac junction). The third lead on the right side is recorded at a level one inch higher (RB-3: main right bronchus at the 'evel of the great vessels).

The catheter is then inserted through the left bronchus. The fourth lead (LBa-1) is recorded with the catheter tip located in the anterior secondary branch of the left lower bronchus at the level of the left leaf of the diaphragm and as near to the cardiac apex as possible. Positions LBm-1 and LBp-1 are located in the middle and posterior branches of the left lower bronchus at the same level. The next lead on the left side (LB-2) is recorded by withdrawing the catheter tip to the level of the pulmonary conus (fig. 6). The sixth position of the tip (LB-3) is one inch higher at the level of the aorta. Similar leads should then be taken with the catheter

* The electrocardiographic instruments employed in this study were the single-channel direct writing Viso-cardiette (Sanborn) and, when available, the three-channel direct writing Technicon machine.

TABLE 1.—*Bronchial Electrocardiographic Exploration*

Case	Sex	Age	Laryngectomy	Routine 12 Lead ECG	Clinical Diagnosis
1. M. M. (figs. 1, 2)	F	61	Yes	Normal	Normal heart
2. S. D.	M	60	Yes	Normal	Normal heart
3. A. S.	M	54	Yes	Normal	Normal heart
4. I. G.	M	39	No	Normal	Normal heart
5. A. W.	M	46	No	Normal	Normal heart
6. J. P. (figs. 3–5)	M	40	No	Normal	Rheumatic heart disease—inactive
7. L. P.	F	20	No	Normal	Rheumatic heart disease—inactive
8. L. S.	F	62	No	Normal	Normal heart

toward reaction during or after the bronchial exploration. During the procedure, sinus tachycardia was usually observed, but a return to normal rate occurred shortly after completion. *No arrhythmia has been observed in any case studied.* This is in sharp contrast to the findings during cardiac catheterization and during routine bronchoscopy.[18, 20, 21, 30–34] Michel and associates[32] reported arrhythmias in 37 per cent of their patients during cardiac catherization.

RESULTS AND DISCUSSION

From our 8 cases of bronchial electrocardiographic exploration (table 1) and the presentation of 2 typical cases (figs. 1–6), we have obtained electrocardiographic patterns corresponding to tracings demonstrated by right and left auricular heart catheterization, by esophageal leads at similar levels and by direct epicardial exploration of the left ventricle.

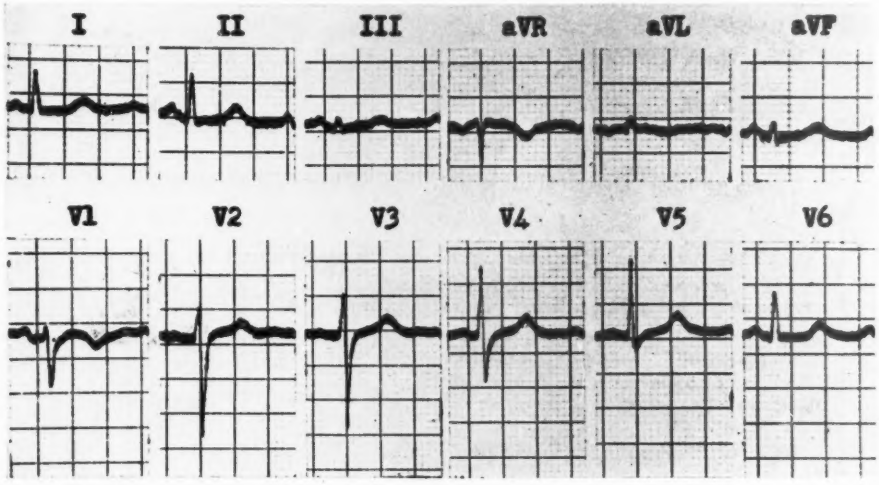

FIG. 1. M.M., female, 61 years of age. Carcinoma of larynx; laryngectomy. Normal heart. Routine 12 lead electrocardiogram normal.

in the middle and posterior branches of both lower bronchi. Our experience shows that exploration may be performed with ease in the anterior, middle and posterior branches of the left lower bronchus. We intend to improve our technic by entering the right middle lobe bronchus which is near the surface of the right ventricle and also the lingula branch of the left upper lobe main bronchus which passes along the anterior surface of the left ventricle. Obviously, leads are taken in positions intermediate between those described. Occasionally tracheal leads may be of additional interest. We observed no un-

In this method, the following factors accounted for variability in potentials recorded: (1) the position and distance of the exploring bronchial electrode in relation to the heart; (2) the position of the heart in the thorax; (3) respiration; (4) possible influence of tachycardia.

When the bronchial exploring electrode was on the right side of the heart, tracings were obtained which are similar to right auricular endocardiograms. Since the electrode was outside

the heart, it was undoubtedly recording potentials from the epicardium of the right heart. The similarity of our tracings to those obtained by right auricular catheterization is in accordance with the generally accepted belief that there is essentially no difference between right auricular endocardiograms and epicardiograms in man. The electrical impulse begins in the sinoauricular node and spreads through the the auricular walls in radiating waves, resulting in similar endocardial and epicardial potentials.[8, 14, 35–38]

We have not had the opportunity to perform simultaneous right heart catheterization and bronchial exploration. Therefore, we compared our findings with those of investigators who have done extensive work in endocardial electrocardiography.

We found three types of P wave in the right bronchial electrocardiograms. These are QS_p, QRS_p, and R_p forms identical with those observed in right auricular endocardiograms. Hence, the spatial relationship of the bronchial electrode to the sinoauricular node is the deter-

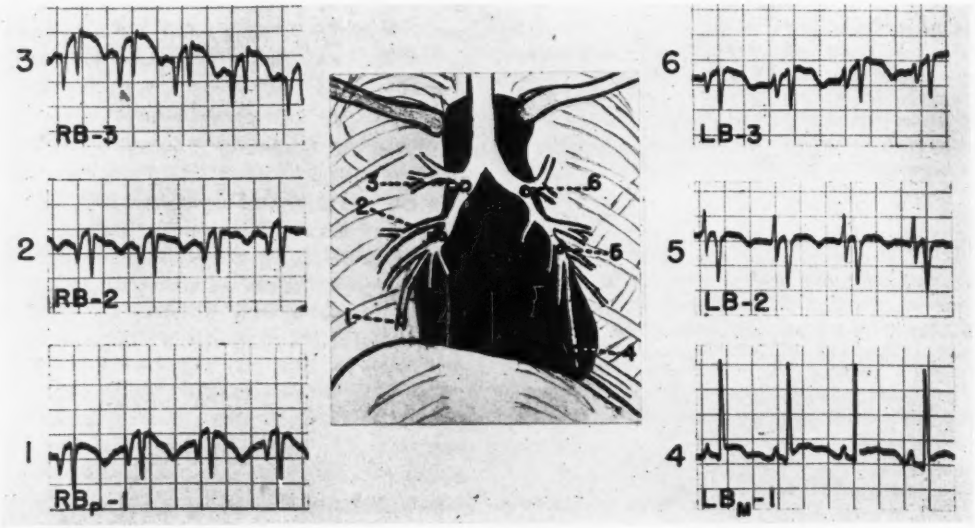

FIG. 2. Same patient as illustrated in figure 1. Detailed bronchial electrocardiographic findings in table 2.

TABLE 2.—*Summary of Findings with Bronchial Electrocardiogram in Patient M. M.**

Bronchial Leads	Position	Location	P	S-Tp	QRS	RS-T	T
Right	RB p-1	Posterior branch of rt. lower bronchus at diaphragm	−	+	rSr′	+	−
Right	RB-2	Rt. bronchus at rt. supracardiac junction	−	+	rSr′	+	−
Right	RB-3	One inch higher than RB2	Deep−	+	rSr′	+	−
Left	LBm-1	Middle branch of left lower bronchus at diaphragm	+	0	qR	+	+
Left	LB-2	Left bronchus near pulmonary conus level	RS	0	QS	Slight +	−
Left	LB-3	One inch higher than LB2	RS	+	rS	+	+−

* See figure 2.

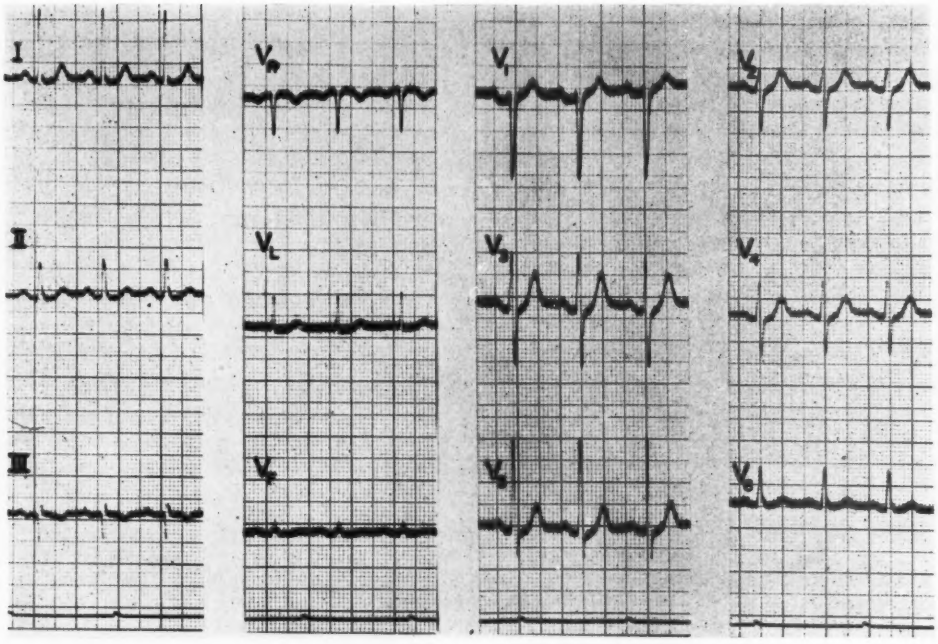

FIG. 3. J.P., male, 40 years of age. Rheumatic heart disease, inactive. Routine 12 lead electrocardiogram within normal limits with slight RS-T depression in leads V_L and V_3 through V_5.

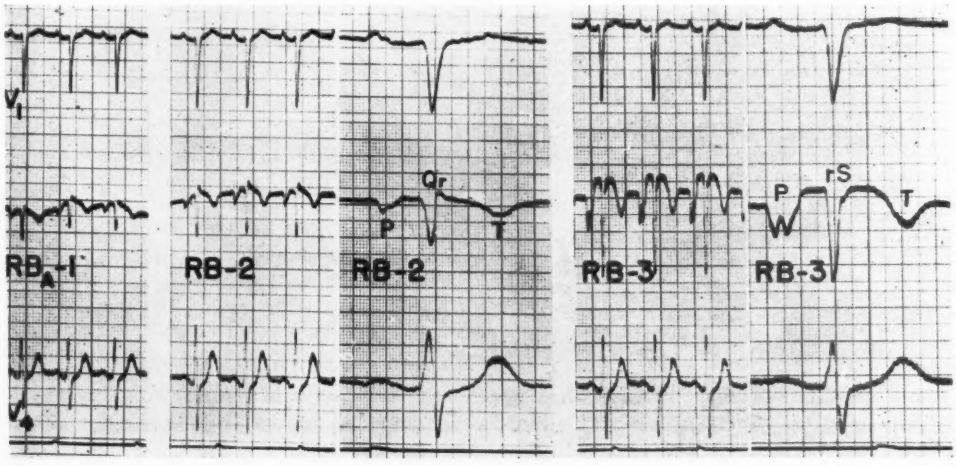

FIG. 4. Same case as illustrated in figure 3. Right bronchial leads with simultaneously recorded leads V_1 and V_4. RBa-1 (in anterior branch of right lower bronchus at diaphragm): RB-2 (right bronchus at right supracardiac junction) and RB-3 (one inch higher than RB-2). Note W-shaped inverted P wave; rS type of QRS complex; elevated S-Tp and RS-T segments in RB-3 representing right cavity potential. RB-2 and RB-3 are recorded both at normal and four times normal speed.

mining factor. The location of the sinoauricular node is difficult to judge on fluoroscopic examination because its location varies with the position of the heart. RB-3 was the only position of the electrode on the right side in which the tip was invariably located above the sinoauricular node. In this position, the P wave was predominantly inverted as in "high" right auricular endocardiograms. We believe that the forms of the P wave in the right bronchial lead can be correlated with corresponding forms of the catheterization leads. Thus, QRS_p or RS_p types correspond more or less to the level of the sinus node. The R_p pattern is recorded when the bronchial electrode is below the sinoauricular node as in "low" right auricular endocardiograms.

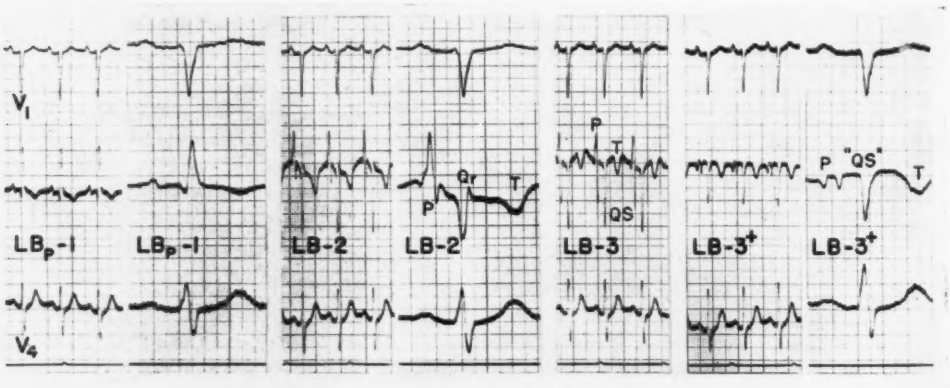

FIG. 5. Same case as illustrated in figure 3. Left bronchial leads. LBp-1 (in posterior branch of left lower bronchus at diaphragm): note qR ventricular complex with inverted T wave (left epicardial lead). LB-2 (in left bronchus near level of pulmonary conus): qRs type P wave of high voltage, S-T_P and RS-T segments are depressed, Qr type of ventricular complex, and inverted T wave (mixed left cavity-epicardial potential). LB-3 (one inch higher than LB-2): qRs type of P wave of high voltage, depressed S-T_P and RS-T segments, QS type of ventricular complex and inverted T wave (true left ventricular cavity potential). LB-3$^+$ (one inch higher than LB-3): W shaped P wave, "QS" ("iso-electric r-deep S") type of QRS and inverted T wave. LB-1, LB-2 and LB-3$^+$ are also recorded at four times normal speed.

In our series the S-T_p segment was frequently above the isoelectric line* (5 cases). This positive displacement of S-T_p segment was also frequently observed in right auricular catheterization electrocardiograms by all investigators. Battro and Biddogia[15] believe it is caused principally by tachycardia which results in acceleration of auricular repolarization. On the other hand, Levine and his associates[20] have convincingly demonstrated in their cases of right heart catheterization that tachycardia and vertical damping of the electrocardiogram are not responsible for the deviation. In their experience the probable factors involved are: (1) current of injury created by contact of the exploring electrode with the endocardium of the right auricle, or (2) a property of the position of the electrode within the right auricular cavity. Of these factors it is our belief that the position of the electrode accounts for the positive displacement of the S-T_p segment in bronchial leads because of the proximity of the electrode to the electrical events of the auricle. However, since the electrode is in contact with the bronchial mucosa, we cannot exclude the possibility of vagovagal reflexes producing a current of injury in the heart through reflex spasm of the coronary arteries. An interesting discussion concerning the clinical value of S-T_p elevation was recently reported by Kossmann and co-workers.[18] Similar S-T_p segment elevation in animals

* The T-P interval was used as the reference line for this study.

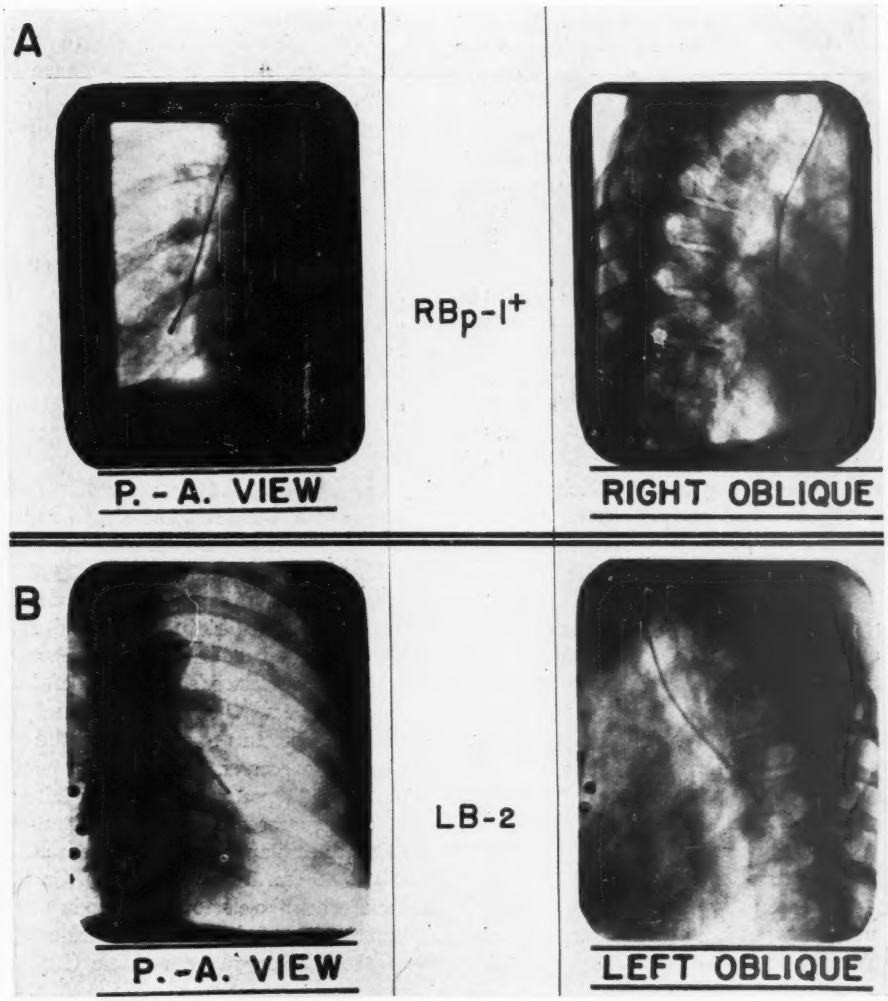

FIG. 6. Spot x-ray films demonstrating bronchial electrode in situ on right and left sides. *A*. RBp-1+ (in posterior branch of right lower bronchus, several inches above the diaphragm): The catheter tip is clearly seen adjacent to the right lateral cardiac border in the posterior-anterior view and to the posterior cardiac border in the right anterior oblique view. *B*. LB-2 (in left lower bronchus below pulmonary conus region): The catheter tip is located at the middle of the left cardiac border in the posterior-anterior view and adjacent to the posterior cardiac border in the left anterior oblique view.

has been described and analyzed by Kisch and associates.[25]

The ventricular complexes in the right bronchial leads simulated those obtained with the intracavity electrode at different levels of the right auricle. In most instances we recorded the rSr′ or QR type which is observed in "high" and "middle" right auricular cavity positions. The ventricular rSr′ and RSR′ are regarded by Hecht[14] as characteristic of "high auricular lead," that is, near or above the sinoauricular node. This investigator noted a consistent similarity between "high auricular lead" and lead V_R and shares the opinion of others that both

of these leads reflect potentials from both ventricular cavities ("mixed potentials"). The deflection r′ or R′ is considered to represent possible terminal depolarization of the base of the right ventricle.

Occasionally, the right bronchial electrocardiogram showed an rS type of ventricular complex which is usually found in "low auricular lead," that is, the pattern inscribed by a right auricular cavity electrode situated near the tricuspid orifice. This rS form is regarded as being characteristic of right ventricular cavity potential by all investigators.

The RS-T segment in right bronchial leads in cases with normal conduction is usually above the isoelectric line from 0.5 to 2 mm.: (a) in RB-1, 5 cases; (b) in RB-2, 3 cases; and (c) in RB-3, 2 cases. The factors which must be considered are the same as those discussed above for the S-T_p segment deviation. In right ventricular catheterization leads, the most frequent cause appears to be current of injury produced by contact o t he exploring electrode with the endocardiumf In right bronchial leads this factor cannot be i.nvolved because the electrode is outside the heart. In our opinion, the major factor of this upward displacement is the superimposition on the RS-T segment of the relatively large T_p wave. A second explanation may be earlier repolarization of the ventricle produced by tachycardia with resultant RS-T elevation as in intracavity leads.

The ventricular T wave in right bronchial leads was in verted in all 8 cases with normal conduction, as in right-sided catheterization of normal hearts.

On the left side, the type of electrocardiogram obtained was dependent on the position of electrode in relationship to the different areas of the left surface of the heart. The P wave in LB-1 position is always upright and of relatively small amplitude. In LB-2 and in LB-3 the P wave was of RS or QRS form in 4 cases; of R form in 3 cases; and of QS form in 1 case, corresponding to the level of the exploring electrode in relation to the sinoauricular node. The P wave in LB-2 and LB-3 was sharp and peaked with high amplitude and in some cases the voltage of the P waves at these levels is equal to that of the ventricular complex or even higher. At the LB-1 position in the few cases in which simultaneous V_1 and V_4 tracings were taken, the peak of the P wave (onset of intrinsicoid auricular deflection) is delayed 0.02 second when compared with V_1, but simultaneous with V_4 (fig. 5). In LB-2 or LB-3 (at the left auricular level), the peak of the P wave (onset of intrinsicoid deflection) appears from 0.03 to 0.04 second later than the P wave peak in leads V_1 and V_4 (fig. 5). An esophageal lead at this level usually shows a delay of intrinsicoid auricular deflection of 0.05 to 0.07 second compared to standard leads.[20] In the bronchial leads, the delay may be shorter because the electrode is closer to the left auricle than the esophageal electrode. The S-T_p segment in the left bronchial leads is either isoelectric or slightly elevated. The factors responsible for the positive deviation of this segment are the same as those discussed for the right bronchial leads.

In LBp-1 the exploring electrode is in the left posterior basal bronchus and in LBm-1 it is in the left medial basal bronchus. In both positions the electrode is near the left leaf of the diaphragm and the ventricular complex is of the qR type. In these positions, the exploring electrode is seen on fluoroscopic examination to be facing the posterior wall of the left ventricle. It thereby records epicardial potentials from this area similar to esophageal leads at this level (30 to 40 cm. from the mouth). On the other hand, when the electrode is deep in the anterior branch of the left lower bronchus and as close to the diaphragm as possible (LBa-1), fluoroscopic examination reveals the electrode to be adjacent to the lateral wall (medial aspect) of the left ventricle. Hence, it usually records potentials from the epicardial surface of this area. In 4 cases, the ventricular complex at LBa-1 was also of the qR type, but of much higher amplitude than in positions LBm-1 and LBp-1. This difference in amplitude of ventricular potentials is related to the fact that in LBa-1 the electrode is either closer to the left ventricle or is in direct line with the main vectorial forces passing through the left ventricular wall.

As the electrode is brought cephalad, there is a progressive increase in the q wave and pro-

gressive diminution of the R wave due to admixture of the left ventricular epicardial and left (or mixed) ventricular cavity potentials. Finally, in LB-2 and LB-3 positions, at the level of the left auricle, *a typical pattern of left ventricular cavity potential* (*QS form*) may be obtained (fig. 2, LB-2, and fig. 5, LB-3). The QR and QS forms of ventricular complex when recorded at these left bronchial positions are similar to the forms of esophageal leads at corresponding levels. In a few cases LB-3 showed a ventricular complex identical with RB-3 (corresponding symmetric position in the right bronchus). In both positions, the electrode is at the base of the heart and faces the ventricular cavities.

In 3 cases, the ventricular complexes in LB-2 and LB-3 were similar to those of LB-1; left ventricular epicardial potentials were recorded at all three positions. We believe that in such cases, despite considerable differences in positions of the electrodes, the vectorial forces traversing the left ventricular wall were of such magnitude and direction that similar complexes were recorded in all three positions. Fluoroscopically, these cases displayed horizontally placed hearts.

Another interesting finding was observed in positions LB-2 and LB-3 in 2 cases. There was a deep "QS" type of ventricular complex. Simultaneous V_1 and V_4 tracings showed that the onset of this deep "QS" in LB-2 and LB-3 began with a delay of 0.01 to 0.02 second, when compared with the onset of the QRS in leads V_1 and V_4 (fig. 5; LB-3$^+$). It is reasonable to assume that the bronchial electrode in such instances was perpendicular to the main direction of excitation of the interventricular septum and therefore the initial portion of the QRS complex was isoelectric. This observation demonstrates the necessity for critical evaluation of any QS form of ventricular complex prior to interpretation of its origin. Only if simultaneously recorded leads demonstrate that the onset of the "QS" is simultaneous with or precedes the onset of the QRS in the reference leads, can one consider this QS to represent pure left ventricular cavity potential.

The ventricular complex in LBa-1 and LBm-1 usually resembled, but was not identical with, that of V_4, V_5, V_6 and aV_L. The type recorded in LBp-1 usually resembled that of the left posterior chest wall (V_8, V_9).

The RS-T segment in LB-1 was isoelectric in 3 cases, below the isoelectric line in 4 cases (depressed 1 to 1.5 mm.) and above the isoelectric line in one case. The RS-T alterations in LB-1 may be contributed to by at least three factors: (1) tachycardia (all our patients had an acceleration of their heart rate) producing a functional coronary insufficiency; (2) a current of injury mediated through a vagovagal reflex from the bronchial mucosa to the endocardium of the left ventricle, which would be manifested by RS-T segment elevation in intracavity leads with corresponding RS-T depression in epicardial leads such as LB-1[39–41]; and (3) the closeness of the exploring electrode to the heart.

At the LB-2 level the RS-T segment was isoelectric in 5 cases and above the isoelectric line in 2 cases. The explanation of this last finding is the same as for the RS-T in the right bronchial lead. At the LB-3 level, there were 4 cases with isoelectric, one case with elevated and one with depressed RS-T segments.

The T wave of the ventricular complex in the LB-1 position was inverted in 4 cases, upright in 2, and flat or diphasic in the remaining 2 cases. Simultaneous leads V_1 and V_4 taken in 1 of the 2 cases with an upright T wave in LB-1 showed an upright T in both precordial leads. In another case, leads V_1 and V_4 recorded simultaneously showed a positive T wave, but LB-1 showed a negative T wave (fig. 5). The T-wave findings can be explained by variation of the vectorial forces of the T wave since the T vector is one of the most sensitive elements of the electrophysical forces of the heart. It may be that because the position of the bronchial electrode is such that it corresponds to the negative side of the T vector in space, a negative T wave is inscribed in the bronchial electrocardiogram with simultaneous positive T wave in V_1 and V_4. Tachycardia is another possible explanation for the inversion of the T wave in LB-1. It may change the hemodynamic factors with diminution of cardiac output, resultant reduced coronary blood flow and change in the direction of the T vector in space. We were unable to take the spatial vector-

cardiogram in all three planes and thus determine the exact position of the T loop in space. We attempted, through the practical technic employed by Grant,[42] to find the spatial direction of the T vector. Of 4 cases studied in this manner, in only 2 could the negative T wave in bronchial leads at LB-1 be adequately explained. The differences noted between left epicardial potentials recorded in bronchial leads and in unipolar chest leads may be of diagnostic significance.

We have illustrated the findings in 2 cases with normal conduction (figs. 1–5). Since left ventricular pathology is of paramount importance and since one can explore the lateral wall of the left ventricle close to its epicardial surface through this method, selected abnormal cases will be investigated, including bundle branch block and intraventricular conduction defects. In these future explorations we shall employ this method in cases where the classic electrocardiographic findings do not coincide with the clinical diagnosis. The patterns in cases of chronic coronary insufficiency with small areas of subendocardial necrosis, previous intramural and high lateral infarction and small "window effects" will be studied. Since this new method of bronchial electrocardiography permits exploration of wide areas of the cardiac surface close to the electrophysical forces, the origin and spread of the electrical potentials of the heart will be further investigated.

Summary and Conclusions

1. We have corroborated that the lung is a suitable electrical conductor.

2. The technic of bronchial electrocardiography is tolerated by patients without much discomfort provided that adequate anesthesia of the bronchial tree has been obtained.

3. In our opinion, unipolar bronchial leads taken with the Wilson technic reflect potentials of the entire heart and not merely those of the myocardium underlying the exploring electrode. The pattern obtained may be influenced by the position of the electrode and its distance from the heart.

4. Leads made with the electrode in the right lower bronchus and in its secondary branches recorded patterns similar to right auricular intracavity potentials taken in man by venous catheterization.

5. In the secondary branches of the left lower bronchus left ventricular epicardial potentials were obtained which corresponded to direct epicardial leads taken in the open chest in man. When the exploring electrode was moved cephalad in the left lower bronchus, a progressive diminution of the R wave with a concomitant increase in the size of the Q wave was noted. When the electrode reached the level of the left auricle, patterns similar to left ventricular cavity potentials (as recorded in man by left heart catheterization and esophageal leads) were obtained.

6. The amplitude of the R wave in leads taken in the left lower bronchus is much higher in the anterior branch than in the posterior branch of this bronchus.

7. Compared with routine unipolar extremity and precordial leads in patients with normal hearts, the right bronchial leads RBa-1 and RBm-1 (in the anterior and middle secondary branches of the right lower lobe) reveal QRS patterns similar to lead aV_R. Lead RBp-1 (posterior secondary branch of the right lower lobe) records potentials similar to leads V_{7R} and V_{8R}. The left bronchial leads reveal in LBa-1 and LBm-1 (the anterior and middle secondary branches of the left lower lobe) a QRS pattern which resembles, but is not identical with, leads aV_L and V_4 to V_7. In LBp-1 (posterior secondary branch of the left lower lobe bronchus) the QRS patterns occasionally resemble those of V_8 and V_9.

8. The RS-T segment in bronchial leads may be elevated or depressed in cases where no RS-T segment alteration is present in routine standard and unipolar leads. The T waves are inverted in all right bronchial leads and usually inverted in left bronchial leads.

9. No arrhythmias were observed in any of the cases studied by bronchial exploration.

10. We believe that our procedure may be employed safely in selected cases, such as patients with chronic coronary insufficiency, previous intramural, high lateral, and small transmural infarcts where the findings in the classical electrocardiogram do not coincide with the clinical diagnosis. The advantage of this method

is that it provides information as obtained partially by cardiac catheterization and esophageal exploration, and that it affords the unique opportunity of exploring widely the surface of the left ventricular wall.

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REFERENCES

[1] SCHAEFER, H.: Elektrophysiologie. Vienna, Wilhelm Maudrich, 1940.

[2] KATZ, L. N., AND KOREY, M.: The manner in which the electrical currents generated by the heart are conducted away. Am. J. Physiol. **111:** 83, 1935.

[3] LEPESCHKIN, E.: Das Elektrokardiogramm. Dresden and Leipzig, Theodor Steinkopff, 1942. P. 172.

[4] CREMER, M.: Über die directe Ableitung der Aktionsströme des menschlichen Herzens vom Ösophagus und über das Elektrokardiogramm des Fetus. München. Med. Wchnschr. **53:** 811, 1906.

[5] LIEBERSON, A., AND LIBERSON, F.: An internal electrocardiographic lead. Proc. Soc. Exper. Biol. & Med. **31:** 441, 1934.

[6] BROWN, W. H.: A study of the esophageal lead in clinical electrocardiography. Part I. The application of the esophageal lead to the human subject with observations on the Ta wave, extrasystoles and bundle-branch block. Am. Heart J. **12:** 1, 1936.

[7] —: Part II. An electrocardiographic study of auricular disorders in the human subject by means of the esophageal lead. Am. Heart J. **12:** 307, 1936.

[8] LEWIS, T., AND ROTHSCHILD, M. A.: The excitatory process in the dog's heart. Part II. The ventricles. Phil. Trans. Roy. Soc. London, s.B. **206:** 181, 1915.

[9] ACKERMANN, L.: Über thorakale Ableitung des elektrokardiogramms. Deutsches Arch. f. klin. Med. **144:** 61, 1924.

[10] WOLFERTH, C. C., AND WOOD, F. C.: The electrocardiographic diagnosis of coronary occlusion by the use of chest leads. Am. J. M. Sc. **183:** 30, 1932.

[11a] WILSON, F. N., WISHART, S. W., AND HERRMAN, G. R.: Factors influencing distribution of potential differences, produced by the heart beat at the surface of the body. Proc. Soc. Exper. Biol. & Med. **23:** 276, 1926.

[11b] —, JOHNSTON, F. D., ROSENBAUM, F. F., ERLANGER, H., KOSSMANN, C. E., HECHT, H. H., COTRIM, N., MENZES DE OLIVEIRA, R., SCARSI, R., AND BARKER, P. S.: The precordial electrocardiogram. Am. Heart J. **27:** 19, 1944.

[12] FORSSMANN, W.: Die Sondierung des rechten Herzens. Klin. Wchnschr. **8:** 2085, 1929.

[13] LENÈGRE, J., AND MAURICE, P.: La dérivation directe, intracavitaire, des courants électriques de l'oreillette et du ventricule droits. Paris méd. **35:** 23, 1945.

[14] HECHT, H. H.: Potential variations of the right auricular and right ventricular cavities in man. Am. Heart J. **32:** 39, 1946.

[15] BATTRO, A., AND BIDOGGIA, H.: Endocardiac electrocardiogram obtained by heart catheterization in the man. Am. Heart J. **33:** 604, 1947.

[16] SODI-PALLARES, D., VIZCAINO, M., SOBERÓN ACEVEDO, J., AND CABRERA, E.: Comparative study of the intracavity potential in man and in dog. Am. Heart J. **33:** 819, 1947.

[17] —, THOMSEN, P., SOBERÓN ACEVEDO, J., FISHLEDER, B. L., ESTANDÍA CANO, A., AND BARBÁTO, E.: El electrocardiograma intracavitario humano. México, Instituto Nacional de Cardiología, 1948.

[18] KOSSMANN, C. E., BERGER, A. R., RADER, B., BRUMLÍK, J., BRILLER, S. A., AND DONNELLY, J. H.: Intracardiac and intravascular potentials resulting from electrical activity of the normal human heart. Circulation **2:** 10, 1950.

[19] DUCHOSAL, P. W., FERRERO, C., DORET, J. P., ANDEREGGEN, P., AND RILLIET, B.: Les potentiels intracardiaques recueillis per cathétérisme chez l'homme. Cardiologia **13:** 113, 1948.

[20] LEVINE, H. D., HELLEMS, H. K., WITTENBORG, M. H., AND DEXTER, L.: Studies in intracardiac electrography in man. I. The potential variations in the right atrium. Am. Heart J. **37:** 46, 1949.

[21] LEVINE, H. D., HELLEMS, H. K., DEXTER, L., AND TUCKER, A. S.: Studies in intracardiac electrography in man. II. The potential variations in the right ventricle. Am. Heart J. **37:** 64, 1949.

[22] NYLIN, B., AND CRAFOORD, C.: Das von Menschen-Herzen in Vivo Simultan von linken und rechten Ventrikel abgeleitete Elektrogramm. Cardiologia **6:** 136, 1942.

[23] ZIMMERMAN, H. A., SCOTT, R. W., AND BECKER, N. D.: Catheterization of the left side of the heart in man. Circulation **3:** 357, 1950.

[24] GROEDEL, F. M., KISCH, B., AND BORCHARDT, P.: The exocardial and endocardial electrogram of the ventricles. An experimental study. Exper. Med. & Surg. **5:** 411, 1947.

[25] KISCH, B., GROEDEL, F. M., AND BORCHARDT, P.: Electrogram of the auricle and great vessels. Exper. Med. & Surg. **5:** 427, 1947.

[26] —: Electrographic investigations of the heart of the fish. Exper. Med. & Surg. **6:** 31 1948.

[27] GROEDEL, M., AND BORCHARDT, P.: Direct Elec-

trocardiography of the Human Heart and Intrathoracic Electrocardiography. New York, Brooklyn Medical Press, 1948.

[28a] SAVJALOFF, V.: Intrapulmonale Ableitungen der Aktionsströme von menschlichen Herzen in Situ. Ztschr. f. Kreislaufforsch. **20:** 584, 1928.

[28b] —: Methode der stereometrische Elektrocardiographie. Ztschr. f. Kreislaufforsch. **21:** 705, 1929.

[29] LANGNER, P. H., AND ATKINS, J. P.: Intrabronchial electrocardiography. A preliminary report. Circulation **2:** 419, 1950.

[30] COURNAND, A., BALDWIN, J. S., AND HIMMELSTEIN, A.: Cardiac catheterization in congenital heart diseases. New York. The Commonwealth Fund, 1949.

[31] DEXTER, L., HAYNES, F. W., BURWELL, C. S., EPPINGER, E. C., SEIBEL, R. E., AND EVANS, J. M.: Studies of congenital heart disease. I. Technique of venous catheterization as a diagnostic procedure. J. Clin. Investigation. **26:** 547, 1947.

[32] MICHEL, J., JOHNSON, A. D., BRIDGES, W. C., LEHMAN, J. H., GREY, F., FIELD, L., AND GREEN D. M.: Arrhythmias during intracardiac catheterization. Circulation **2:** 240, 1950.

[33] BRUCE, R. A., YU, P. N. G., LOVEJOY, F. W., MCDOWELL, M. E., AND PEARSON, R.: Ventricular tachycardia during cardiac catheterization of patient with Wolff-Parkinson-White Syndrome. Circulation **2:** 245, 1950.

[34] BURSTEIN, C. L., LOPINTO, F. J., AND NEWMAN, W.: Electrocardiographic studies during endotracheal intubation. I. Effects during usual routine technics. Anesthesiology **11:** 224, 1950.

[35] WILSON, F. N., MACLEOD, A. G., AND BARKER, P. S.: The Distribution of the Currents of Action and of Injury Displayed by Heart Muscle and other Excitable Tissues. Ann Arbor, University of Michigan Press, 1933.

[36] MACLEOD, A. G.: The electrocardiogram of the cardiac muscle. An analysis which explains the regression of the T deflection. Am. Heart J. **15:** 165, 1938.

[37] BAYLEY, R. H.: The potential produced by cardiac muscle. A general and a particular solution. Proc. Soc. Exper. Biol. & Med. **42:** 699, 1939.

[38] MACLEOD, A. G., AND COHEN, E. A.: A new piezoelectric manometer to record intracardiac pressures and for the simultaneous recording of intracardiac electrograms. Am. Heart J. **21:** 345, 1941.

[39] KISCH, B.: The influence of surface of heart muscle on the electrocardiogram. Cardiologia **4:** 304, 1940.

[40] —: Multiple chest leads in localized damage of the heart. Exper. Med. & Surg. **3:** 154, 1945.

[41] WOLFERTH, C. C., BELLET, S., LIVEZEY, M. M., AND MURPHY, F. D.: Negative displacement of the RS-T segment in the electrocardiogram and its relationship to positive displacement. An experimental study. Am. Heart J. **29:** 220, 1945.

[42] GRANT, R. P.: The relationship of unipolar direct leads to the electrical field of the heart. Circulation **1:** 878, 1950.

[43] GIBERT QUERALTO, J.: Electrocardiographie intracardiaque gauche. Semaine d. hôp. Paris **26:** 3287, 1950.

[44] BARKER, P. S., MACLEOD, A. G., ALEXANDER, J., AND WILSON, F. N.: The excitatory process observed in the exposed human heart. Tr. A. Am. Physicians **44:** 125, 1929.

On Evaluating the Einthoven Triangle Theory

By J. Scott Butterworth, M.D., and John J. Thorpe, M.D.

The authors have attempted to treat a controversial subject in a different way by introducing a known potential into the cavity of the living human heart and determining the magnitude of this potential at the extremities. While the data may be subject to various interpretations it is suggested that this technic may be a valuable tool for further analysis of the spread of potentials in the body.

THE VALIDITY of the Einthoven triangle theory has aroused considerable controversy among students of electrocardiography for a generation. A variety of methods have been used in an effort to prove or disprove the assertion that the triangle formed by the three standard leads of the electrocardiogram conforms to Einthoven's postulates. The work of Wilson and his coworkers[1] in studying the spread of currents from electrodes placed in the cardiac area in the human cadaver stimulated us to perform experiments of a somewhat similar nature with electrodes situated on the surface of the body between which potentials could be impressed. These experiments were performed with single make and break shocks. Similar experiments performed with 25 cycle alternating current have recently been reported by Wilson.[2] Our studies revealed that there were certain points on the anterior and posterior surfaces of the thorax between which make and break shocks produced no resultant deflections in any of the standard leads of the electrocardiogram. (The electrocardiograph patterns in each lead were disregarded.) When, however, the electrodes were moved even slightly away from these points, deflections resulted in the standard leads. These isoelectric points varied slightly in position from one individual to another, but in general, the anterior position was slightly above the xyphoid process in the midline and the posterior position was almost exactly opposite on the back.

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Although these experiments indicated that the electrical center of the triangle formed by the three standard leads approximated the position of the heart, we were unable to exclude the possibility that the current was traveling over some special pathway through the skin or subcutaneous tissues and that our findings localized the isoelectric point of these tissues rather than to that of the heart. The logical solution to this difficulty appeared to be the introduction of suitable electrical impulses within the heart itself. For this purpose we had made a special solid cardiac catheter* containing two insulated electrodes at its distal end. One electrode was situated at the tip of the catheter but was buried slightly so that it would not actually contact any cardiac structure. The second electrode was similarly buried at the side of the catheter 2.5 cm. proximal to the tip. The catheter was tested by placing it within the right ventricle of animals and introducing potentials up to 4.5 volts between the electrodes. No untoward events occurred, such as the production of arrhythmias, so it was considered safe to proceed with human subjects.

The first experiment was performed on October 28, 1948. The special catheter was inserted into the left antecubital vein and threaded forward into the right auricle under fluoroscopic control. The continuity of the electrodes was tested by taking endocardial electrocardiograms. Unfortunately, one lead had been damaged during sterilization and was not usable. The experiment was continued by attaching the intact electrode to one side of the circuit and the other side of the circuit was attached to a lead to (1) the left leg and

* U. S. Catheter Corporation

(2) the right arm. The resistance between the endocardial electrode and the extremities was constant. An initial reference impulse of 0.05 volt was used. Deflections were recorded in the standard leads and augmented extremity leads by a Cambridge Simplitrol Electrocardiograph but were of such small magnitude that quantitative measurement was difficult. (The patterns from the heart were disregarded.) For this reason the reference current was increased to 0.10 volt. Table 1 lists the recorded and corrected values of these deflections.

With a known direction of current from the heart to the leg or in the reverse direction (90 or 270 degrees from the horizontal plane) one

TABLE 1.

Lead	Standardization		Recorded Deflections	Corrected Deflections
	cm.			mv.
I	1.4	Make	±0	0
		Break	0	0
II	1.4	Make	−1.1	−0.79
		Break	+1.1	+0.79
III	1.5	Make	−1.3	−0.87
		Break	+1.2	+0.80
aV_R	0.90	Make	+0.35	+0.39
		Break	−0.35	−0.39
aV_L	0.95	Make	+0.35	+0.37
		Break	−0.35	−0.37
aV_F	0.95	Make	−0.70	−0.74
		Break	+0.70	+0.74

Voltage = 0.10 volt

would expect Lead I to pick up little or no potential change and leads II and III to be equal. The recorded deflections confirm this. Similarly aV_R and aV_L should be approximately equal and aV_F should be double the value of either of the others. The recorded deflections are in accord and the sum of the extremity potentials approximates zero.

Table 2 lists the deflections recorded when 0.1 volt was used in a circuit between the endocardial electrode and the right arm electrode.

Calculation of the direction of the vector of this current reveals it to be 36 (or 216) degrees which corresponds well with the observed anatomic axis from the point of the catheter in the right auricle to the right shoulder. (An exact anatomic axis could not be accurately measured as it would have been difficult to know which point on the right shoulder to use for reference.)

The second experiment was performed on June 22, 1949. The double endocardial electrode

TABLE 2.

Lead	Standardization		Recorded Deflections	Corrected Deflections
	cm.			mv.
I	1.4	Make	+3.2	+2.3
		Break	−3.3	−2.3
II	1.35	Make	+3.45	+2.6
		Break	over 2.3	—
III	1.5	Make	+0.25	+0.17
		Break	−0.25	−0.17
aV_R	0.9	Make	−2.5	−2.8
		Break	+2.5	+2 8
aV_L	0.9	Make	+1.1	+1.2
		Break	−1.2	−1.3
aV_F	0.9	Make	+1.3	+1.4
		Break	−1.3	−1.4

Voltage = 0.10

TABLE 3.

Lead	Standardization		Recorded Deflections
			mv.
I	1.0	Make	−0.07
		Break	+0.07
II	1.0	Make	−0.45
		Break	+0.45
III	1.0	Make	−0.40
		Break	+0.40
aV_R	1.0	Make	+0.25
		Break	−0.25
aV_L	1.0	Make	+0.15
		Break	−0.15
aV_F	1.0	Make	−0.40
		Break	+0.40

Voltage = 1.35 volts

was inserted into the midportion of the right auricle by way of the antecubital vein. The resistance between the two electrodes was 25,000 ohms. Beginning with 0.08 volt and increasing, suitable deflections were produced on the Cambridge Simpli-scribe electrocardiograph using 1.35 volts. The axis of the catheter was recorded by a spot x-ray film. A reference opaque wire was placed in a vertical axis to the right and parallel to the sternum. Table 3 lists

the recorded values of these deflections. Inasmuch as the standardization was 1.0 cm. throughout, no corrected values are necessary. Calculation of the vector indicates it to be approximately 88 degrees which corresponded within the limits of error to the anatomic axis of the electrodes as observed by x-ray. (It is extremely difficult to determine an exact anatomic axis from a spot film because of such variable factors as the position of the central beam in relation to the plane of the catheter and the plane of the reference vertical line.)

Discussion

We have recently become acquainted with the work of Hafkenschiel and associates[3] in which they introduced 25 cycle alternating current into the right ventricular cavity of dogs. Ventricular fibrillation resulted in the animals with input currents between 1 and 2½ milliamperes. Certain differences exist between these experiments and those reported in this paper. First, we have used make and break shocks at irregular intervals but not oftener than about once per second. Secondly, we used a special catheter in which both electrodes were so located that neither one could come into contact with the endocardium. In the experiments of Hafkenschiel and co-workers the electrodes were silver bands around the circumference of the distal end of the catheter and it would seem that one or both electrodes touched some part of the endocardium. We feel that these differences might very well account for the fact that we never observed any arrhythmias in either animal or human cases. While we have had no difficulties in our limited experience, we would emphasize that it is probably very important that the electrodes be prevented from coming into actual contact with any cardiac structure. The difference between the use of make and break shocks and alternating current of various cycle frequencies remains to be studied.

These experiments are of such limited scope that the results do not warrant detailed analysis. We do not feel that they offer, at present, a definite solution of whether or not the body acts as a homogeneous volume conductor and obeys all of Einthoven's postulates. On the other hand, the potentials introduced within the heart seem to spread to the surface of the body in such a way that the resultant deflections correspond within the limits of error to the predictions based upon Einthoven's theory.

Summary and Conclusions

By means of a special double electrode cardiac catheter make and break shocks of low voltage were introduced within the human heart. The deflections resulting at the surface of the body were recorded by a Cambridge string galvanometer or Simpli-scribe in the standard leads and the augmented extremity potentials. Calculation of the vectors of these currents indicated close conformity with the anatomic axis of the electrodes.

It is felt that these experiments, while of a preliminary nature, seem to conform within the limits of error to Einthoven's theory. A more detailed study of many cases will be necessary to definitely establish such relationships. The method, though still subject to improvement and further investigation, should be a useful tool in investigating the theory of unipolar electrocardiography and spatial vectors.

REFERENCES

[1] Wilson, F. N., Johnston, F. D., Rosenbaum, F. F., and Barker, P. S.: On Einthoven's triangle, the theory of unipolar electrocardiographic leads, and the interpretation of the precordial electrocardiogram. Am. Heart J. **32:** 277, 1946.

[2] Wilson, F. N., Bryant, N. M., and Johnston, F. D.: On the possibility of constructing an einthoven triangle for a given subject. Am. Heart J. **37:** 493, 1949.

[3] Hafkenschiel, J. H., Neumann, A. J., Kay, C. F., Foltz, E. L., Talley, D. D., and Zinsser, H. F.: A method of studying the attenuation of alternating sinusoidal currents introduced into the heart in life and death. Am. J. M. Sc. **219:** 583, 1950.

CLINICAL PROGRESS

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Clinical Aspects of Mercurial Diuretics

By C. THORPE RAY, M.D., AND GEORGE E. BURCH, M.D.

FROM the standpoint of the volume of literature, diversity of therapeutic indications and duration of use, mercury in its various forms has no equal among the commonly used drugs of today. Inorganic mercury was employed for its diuretic properties in the sixteenth century.[1] Many references have been made to the combined use of digitalis and mercurous chloride. However, the policy of continuing the administration of mercury until stomatitis appeared was responsible for a decline in its popularity until fairly recently. There were no really significant advances in the use of mercurial diuretics until 1917, when an organic mercurial compound, Novasurol (the double salt of sodium mercurichlorphenyl oxyacetate with diethyl barbituric acid), was introduced by Zeiler as an antisyphilitic agent. In 1920 Saxl and Heilig[2] first reported an accidental observation on the efficacy of Novasurol as a diuretic.

Extensive search for organic mercurial diuretics of less toxicity resulted in the introduction of several such compounds. Of the more commonly used preparations, Salyrgan (sodium [*o*-(hydroxy-mercuric-methoxylpropyl carbamyl) phenoxy]-acetate) was introduced in 1924, then Mercupurin (Mercuzanthin; sodium trimethyl - cyclopentane - dicarbonic acid - methoxy - mercury - allylamide - theophylline), Mercuhydrin (sodium salt of methoxy-oxymercuripropylsuccinylurea with theophylline) and Thiomerin [disodium salt of N - (γ - carboxymethylmercaptomercuri - β - methoxy) propyl camphoric acid] (mercaptomerin sodium), the latest. The introduction of theophylline or a thiol group into the molecule reduced the toxicity without disturbing the diuretic effect of the mercury. The quantity of mercury and the manner in which it is bound in these compounds varies slightly. For example, Mercuzanthin and Salyrgan contain 37 to 42 per cent mercury by weight, Mercuhydrin 39 mg. per cc. and Thiomerin 40 mg.

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CHEMISTRY

The chemical properties of mercury determine its biologic actions. For example, the local effect of mercury depends upon the concentration of mercurial ions. Highly ionized inorganic compounds exert greater toxic effects on tissues than do the less ionizable organic mercurial compounds.[3] Solubility of the various mercurial compounds influences the rate of absorption and, in turn, the activity. Their solubility varies with the chemical medium, being less soluble in aqueous solutions containing low concentrations of protein than in those containing large quantities of protein. This latter condition exists in the body in the presence of therapeutic amounts of mercury and affects the rate of absorption from the site of injection. The chemical environment afforded by the body influences the phenomena of solubility, ionization and diffusion,[3, 4] all of which influence the pharmacologic effects of mercury.

The chemical form in which mercury of a

mercurial diuretic exists after injection into man has not been definitely established. Although protein binding of mercury has been demonstrated in vitro and in vivo, this does not exclude the existence of mercury in some combination other than with protein. The ionization equilibrium of protein mercurial complexes which exist in the body is also unknown. Rates of diffusion are certainly influenced by binding of mercury to large protein molecules, and alterations in diffusion affect some of the physiologic responses of the body to injection of mercury. It has been shown[4] that under chemical conditions which exist in the body diffusion of mercury may be enhanced. The strong affinity of mercury and other heavy metals for thiol groups has been demonstrated,[5] but it has not been established that the action of mercury in the body is mediated through reactions with thiol-containing compounds.

The active principle of all mercurial diuretics is the mercury ion. The diuretic action has been demonstrated to be alike for ionizable inorganic mercury, organic mercurials and colloidal mercury,[6] though they vary considerably in toxic properties. The rate, duration and amount of diuresis vary with the particular compound of mercury. Per unit weight of mercury, the highly ionizable compounds are more potent diuretic agents than are the organic mercurial compounds.

Pharmacodynamics

Detailed study of the metabolism of mercury in the body has been hampered by the rather cumbersome and insensitive chemical methods for mercurial analysis. Most methods involve digestion of the organic materials in the presence of reducing agents. Through volatilization of mercury, large amounts may be lost by such technics.

Absorption

Mercury may be absorbed by way of the respiratory and gastrointestinal tracts, the skin, vagina and subcutaneous tissues.[3, 7] The unpredictable nature of the absorption of mercury administered orally and rectally[3, 9] make these routes less dependable. The parenteral route is the most predictable and dependable. Absorption is rapid and satisfactory following intramuscular injection.[10] The presence of theophylline greatly hastens absorption from muscle; DeGraff and associates[10] found that approximately 80 per cent of the injected mercury had been absorbed within 30 minutes and 97 per cent at the end of one hour. Mercupurin and Salyrgan without theophylline were absorbed much more slowly; at the end of 4 hours 50 per cent remained, and at the end of 48 hours about 10 to 20 per cent of the mercury remained at the site of injection. Absorption from edematous or adipose tissue is much less rapid and may result in local reaction. Thiomerin apparently is absorbed satisfactorily from subcutaneous tissue; the curve of absorption from muscle is similar to that for Mercuzanthin and Salyrgan.[11] Mercurial diuretics are absorbed slowly from ascitic fluid.

Studies of transfer of radiomercury of a labeled mercurial diuretic across a blister membrane revealed a reduction in transfer by protein binding of the mercury. The mercury was absorbed more slowly when suspended in a protein medium. No differences existed in rate of absorption or transfer in normal controls and in subjects with congestive heart failure. Elevation of venous pressure by inflating a cuff around the arm had no effect on the rate of absorption.[12]

Distribution

Distribution of mercury throughout the body depends upon the form of the mercurial compound administered and the duration and route of administration. In mercurial poisoning, distribution of mercury in the body may be influenced by "overloading" or injury of the potential mercurial excretory mechanisms. The concentration of mercury attained in the tissues is certainly affected by failure of renal excretion. The excretion, distribution and storage of mercury in the body after a long course of inunction treatments is different from that observed after the single injection usually given for its diuretic effect. With inunction the body is brought into a state of "saturation" by frequent small doses; there is

storage of mercury throughout the body; excretion reaches a maximum at two to three weeks and may continue for 60 days or more after administration has been discontinued.[13] Following oral administration of a mercurial diuretic over a period of four days, there may be continued excretion in the urine for 16 additional days.[14] Such observations indicate that mercury is stored in the body.

Following a single intravenous injection, there is no "state of saturation" nor is equilibrium of distribution achieved if the kidneys are normal. Excretion is so rapid that the observed regression of mercury in the blood is attributable largely to renal excretion. There may be some storage after intravenous injection but it is relatively small by comparison with that following inunction treatments of syphilis, in which about 50 per cent of the administered mercury may be stored.

Mercury is widely distributed in the body. It has been found in almost every organ, including bone. The highest concentration is found in the kidney and the next highest in the liver. It appears in the urine in highest concentrations and in the bile in relatively high concentration. Maximum concentration in the bile is delayed many hours after the peak concentration in the blood is reached. After continuous administration, as by inunction, concentration in the bile may be higher than in the blood, but after a single intravenous injection, the relative concentration depends entirely upon the time of sampling. Thus, if sampling were made 24 hours after injection, when blood concentration is low, concentration in the bile might be higher. This is not true in the hours immediately following the injection.

After a single intravenous injection of a mercurial diuretic labeled with radioactive mercury, this element was found to enter ascitic, pleural and edema fluid and sputum slowly. None was found in sweat, gastric juice or spinal fluid. Washed human red blood cells contained no mercury. The fecal content of mercury varied widely from 0.01 to 26 per cent after intravenous administration of labeled Mercuhydrin.[15]

Immediately after intravenous administration of a mercurial diuretic, concentration of mercury in the blood declines rapidly. If there is renal insufficiency, however, it remains elevated, and the distribution of mercury in the body differs from that found when the kidneys are normal. With normal renal function there is a large unidirectional shift of mercury into the urine. This shift is so rapid that little time is available for the relatively slowly diffusing mercury-protein complex to reach equilibrium of distribution throughout the body. If the kidneys fail to excrete the mercury, equilibrium of distribution may be attained. The extracellular fluid compartment in states of generalized edema may serve as a large storage depot for mercury.

The form in which mercury is stored in the body is unknown, but it is thought by some to be in combination with tissue proteins. This "stored" mercury may remain in the body for varying lengths of time. As with storage of lead, certain chemical environments, such as a high pH, encourage deposition of mercury, whereas acid precursors favor mobilization from storage depots. The concentration of mercury in the blood may be modified by factors which affect storage equilibrium.

Excretion

Although the principal avenue of excretion of mercury from the body is normally by way of the urine, it may occur by way of the saliva, bile, and intestinal mucosa and thus appear in the feces. The latter route becomes more important when the kidneys are diseased or have been injured by an overload of mercury.

The chemical state in which mercury is excreted is unknown. It may be excreted in different chemical forms in the stool and urine, and these forms may vary with time in either of these avenues of excretion. The extent to which the excreted mercurial compound may be influenced by the chemical state in which it is administered, such as the bichloride, succinate, salicylate, colloidal mercury or the organic mercurial diuretics, has not been determined, nor has it been definitely established that mercury is excreted as the same compound in which it was administered.

The pattern of renal excretion for mercury is influenced by the route and duration of

administration and by the rate of absorption. The excretory pattern of mercury administered slowly to the point of saturation is a gradual increase up to a maximum at the end of two to three weeks. The dosage and the blood concentration determine the amount excreted. The "saturation point" of the blood is reported to be 3 mg. per liter[7]; when this level is exceeded, excretion occurs. With the large storage depots in the body, excretion may continue for as long as six months after therapy has been discontinued. Huffman[14] observed urinary excretion for as long as 16 days after oral administration for four days. The time-course of excretion of mercury in urine following oral administration of a diuretic labeled with radiomercury has been described by Overman and associates.[9] This involves the variable of intestinal absorption, but the peak excretion of mercury in the urine occurred at approximately 200 minutes after ingestion. Of the mercury which was recovered in the urine, approximately 50 per cent was recovered in the first 400 minutes after administration of the capsules. The last 20 per cent was recovered between 600 to 1500 minutes after ingestion.

Excretion of mercury is most rapid immediately after intravenous or intramuscular injection. The rate and completeness of excretion of the various diuretics are essentially the same. In the presence of normal kidneys, urinary excretion of intravenously administered mercury has been found to be complete in from 24 to as long as 72 hours. Excretion of the last 10 to 20 per cent occurs so slowly that the complete time-course of urinary excretion is difficult to establish by the relatively insensitive chemical methods of analysis for mercury.

Previous studies[6] indicated a qualitative directional similarity in practically all of the curves between urinary volume, excretion of mercury and concentration of mercury for a variety of mercurial compounds, organic and inorganic. Excretion reached a peak in one to two hours after injection and then descended as a parabolic curve. Curves for mean urinary excretion after intravenous injection were almost identical for many of the mercurial compounds. Diuresis following intramuscular injection was not materially slower than following intravenous injection, but the excretion of mercury was.

The time-course of renal excretion has been studied by means of a mercurial diuretic labeled with radiomercury.[16, 17] After intravenous injection the mercury appeared at the tip of a ureteral catheter in three and one-half to five minutes but the peak concentration was not reached until approximately 20 minutes after injection. The lag in time between renal excretion and extraction of mercury from the serum reflects retention within the kidney. The rate of excretion is slower in subjects with congestive heart failure than in normal subjects and is slower still in those with renal insufficiency, tending to vary indirectly with the degree of renal failure. The time required for one-half of all the administered mercury to be excreted in the urine serves as an index of the differences among normal and diseased subjects. Normal subjects excrete half the administered mercury in about two hours, whether it is given intravenously or intramuscularly; yet some mercury is usually still present in the urine at the end of 24 hours. In some subjects with congestive heart failure more than twice as long is required for excretion of one-half the administered mercury, the time varying considerably with the state of the failure. Renal insufficiency may result in extreme retardation of excretion of mercury. In one subject only 19 per cent was excreted in eight days, although there was a large volume of hyposthenuric urine during this time. It is therefore not correct to assume that excretion is complete in 24 hours simply because urinary volume is large. Daily administration may result in an accumulation of mercury in the body of normal subjects and an even greater accumulation in the presence of disease states such as congestive heart failure and renal insufficiency.

Site and Mode of Action

It has not been definitely established whether mercury possesses extrarenal actions which influence diuresis. Refractometric and blood chemical studies yield findings of hemodilution compatible with extrarenal action. There is, however, no evidence of mobilization

of fluids with consequent hemodilution before mercurial diuresis occurs. It is difficult to understand why purely renal action should be associated with hemodilution, since water and electrolytes should enter the circulation no faster than they are removed by the kidneys, were their migration determined entirely by renal excretion and renal action.

Renal effects of mercurial diuretics have been studied rather extensively. When small amounts of mercury were injected into one renal artery, diuresis ensued from the "injected" kidney only.[18] With increasing doses of mercury, diuresis from the opposite kidney developed. Presumably, the extracting capacity of the injected kidney having been exceeded, the excess mercury gained access to the other kidney by way of the blood stream. These observations and those of Govaerts[19] that a kidney taken from an animal at the height of mercurial diuresis continues to reveal diuresis when transplanted into the neck of an untreated animal indicate that the action of mercury can be due solely to direct action upon the kidney. However, extrarenal effects have not been excluded. Such extrarenal changes associated with mercurial diuresis as alteration in size of the extremities and rise in blood pressure may influence the diuretic action of mercury.

The precise site and mode of action of mercury in the kidney have received some attention but neither has yet been definitely ascertained. Abundant evidence tends to indicate that the rate of glomerular filtration is not increased by mercurial diuretics alone. When a xanthine is combined with the mercurial diuretic, there may be a slight rise in rate of glomerular filtration, but it is not considered to be of sufficient magnitude to explain the observed diuresis. Furthermore, if the mercurial diuretics are given in extremely large doses, the rate of glomerular filtration may decline.

Increased urinary excretion of electrolytes and water without antecedent measurable changes in their blood concentration nor significant changes in rate of glomerular filtration supports the concept of a tubular site of action of mercury. Micropuncture studies indicate that mercury "abolished the power of active reabsorption and power of selective retention of diffusable substances by the renal tubule."[20] Many experimental and clinical investigations have demonstrated reduction of tubular reabsorption with resultant increase in urinary excretion of electrolytes and water, the precise mechanism being unknown. Speculation has been directed at alterations in certain enzymatic processes in the tubular cells which are concerned with transport and selective reabsorption of electrolytes. Mercury has been shown to inactivate certain enzyme systems which may be reactivated by BAL.

Several of the specific functions of the kidneys have been studied during mercurial diuresis: tubular maximum excretory capacity for glucose (Tm), glomerular filtration, renal paraaminohippurate extraction and renal clearances of mannitol, sodium, chloride and uric acid. Weston and associates[21] obtained a depression of glucose Tm and PAH extraction following mercury. Tm_{PAH} was depressed and a decrease of 40 to 80 per cent in Tm_g at the time of maximal electrolyte excretion occurred. Apparently mercury depresses specific proximal tubular function and glucose reabsorption in man. Differences in response between man and dog have been observed.[22] Because of species differences in renal function, correlation and application of data should be made cautiously when different animals are under consideration.

The site of action of the mercurial diuretics has been suggested to be the distal tubule rather than the proximal segment or both.[23, 24] In dogs prepared by saline infusion before and after injection of mercury the sodium excretion was intensified with increasing doses of mercury up to a certain point, beyond which added increments of mercury had no additional effect. With larger doses, the peak of sodium diuresis was reached more quickly. The existence of an upper level of sodium excretion, regardless of the dose of mercury, suggested that only a fraction of renal tubular reabsorptive function was "mercury sensitive." This fraction has been estimated to be approximately 15 per cent of that reabsorbed during the control periods, a value compatible with the view that 80 to 85 per cent is reabsorbed

in mercury-insensitive proximal tubules. Because mercury and Pitressin combined did not increase excretion of sodium beyond that obtained with mercury alone, it was concluded that both acted at the same site, the distal segment. The investigators were of the opinion that mercury influences sodium reabsorption in the proximal tubules only when the dose of mercury is sufficient to produce tissue damage.

For numerous reasons it cannot be concluded from these experiments that mercurial diuretics act solely on the distal tubule in man. Experiments were carried out on dogs, which were receiving large amounts of normal saline, the dosage of mercury was large, the difference between therapeutic and toxic levels of mercury cannot be definitely differentiated, and broad assumptions were made by the investigators in order to reach this conclusion.

The most striking response to injection of mercury is the diuretic effect, which is usually complete in 24 hours but occasionally may last as long as 48 hours. The volume of urine excreted varies widely, ranging from 1 to 3 liters, but occasionally as much as 15 liters of urine are passed by patients with anasarca. The specific gravity is lowered for the duration of the diuresis.

More striking than the water diuresis is the preceding outpouring of electrolytes in the urine. Excretion of chloride, sodium, potassium and magnesium is increased, whereas excretion of phosphates and sulfates is not particularly affected.[25] The electrolyte excretion depends upon the concentration of chloride and sodium in the blood, since hyponatremia and hypochloremia are associated with little or no diuretic response.[26] Following excessive outpouring of sodium, chloride, potassium and water, there is usually decreased excretion of these substances for one to three days or until normal water and electrolyte balance is restored.[25]

As a result of excretion of large amounts of electrolytes and water, certain chemical changes occur in the blood. Concentration of chloride in serum and extracellular fluid usually declines and that of the bicarbonate rises, that of sodium remaining essentially unchanged.[27] Concentration of sodium in the extracellular fluid has been reported to be low in some instances after administration of mercurial diuretics, depending largely upon previous concentration and intake of sodium. Schwartz and Wallace[27] found a greater negative balance of chloride than of sodium. Potassium appeared in the urine in greater concentration than could be explained on the basis of its concentration in the extracellular fluid. Additional observations are required to define these effects more precisely, especially for potassium.

The diuretic response to injection of mercury is conditioned by the electrolyte concentration in the body and, therefore, may be influenced by premedication with acidifying salts. The diuretic response may be increased by any measures which enhance renal blood flow and rate of glomerular filtration, such as bed rest and administration of xanthines.

There are many physiologic responses to the intravenous injection of a mercurial diuretic besides excretion of sodium and water. Blood pressure may increase occasionally because of generalized vasoconstriction. The volume of the limbs and of the kidney has been observed to decline, accompanied by a transient decline in renal blood flow with resultant transient antidiuretic effect.[28] Changes of hemoconcentration and hemodilution are inconstant. Blood urea is not characteristically altered; it may rise, fall or remain unchanged.

Toxicity

Mercury has long been recognized as a protoplasmic poison. In this respect, the more highly ionized the mercurial compound is, the more toxic it is. Mercury exerts a local toxic effect at the site of contact with the tissues. Gastrointestinal symptoms of nausea, vomiting, abdominal pain and diarrhea, which is occasionally bloody, attest to the toxic local action of mercury when taken orally. Proctitis and ulceration in the rectum may appear when mercurial diuretics are administered as suppositories. Their local irritant effect when given intramuscularly or subcutaneously is well established. It is reduced slightly by the presence of the xanthines and is considerably diminished by the presence of thiol groups.

After mercury gains access to the body, it

tends to become more concentrated in certain organs, although its action is widespread. It is known that large doses of mercury result in necrotic changes in the tubular epithelium of the kidney, and in animals smaller doses acting over a long period of time produce the same changes.[29] The question of damage to the renal tubular epithelium from prolonged frequent injections of therapeutic amounts of the mercurial diuretic has been posed. Enough experience has been accumulated to indicate that mercury may be used in amounts adequate to achieve a diuretic effect without apparent injury. Renal function tests and histologic examination of the kidneys in subjects who had received large quantities of mercurial diuretics have rarely revealed any damage. Occasionally the kidney may exhibit tubular damage following intravenous injection of a mercurial diuretic in the usual doses. When large doses of mercury are administered, toxic changes may also occur in the liver.

Certain differences in reaction to mercurials are known to exist among different species. In animal experiments, amounts of mercury comparable to those used for diuresis in man may produce transient or permanent renal damage. In rats, proteinuria due to injection of a foreign albumin was found to increase renal tubular toxicity of mercury when the mercury and albumin were administered simultaneously. When protein was given prior to the mercury, a protective action resulted.[30] The clinical significance of these observations has not been established.

Toxic reactions of the cardiovascular system to intravenous injection of a mercurial diuretic are more important clinically. The cardiovascular response varies with different dosages of mercury. Generalized vasoconstriction and more serious reactions are blocked by glutathione, cysteine and BAL.[28]

One of the most frequent cardiac manifestations of toxicity is a disturbance in cardiac mechanism. Animals exhibit considerable species differences in susceptibility to the cardiotoxic action of mercury. Dilutions of either organic or inorganic preparations of mercury of 1 to 100,000 or greater were sufficient to produce heart block in the turtle; this was reversed by sodium thiosulfate.[31] Farah and his associates[28, 32] found that the monothiols, cysteine and glutathione and dithiol BAL increased the half lethal dose in cats, dogs and mice. Heart failure produced in a heart-lung preparation by infusion of Salyrgan was reversed by these compounds. Large amounts of mercury produced a rapid fall in blood pressure.

Other attempts have been made to protect the cardiovascular system against the toxic action of mercury. Pines and associates[33] were able to reduce the incidence of ventricular fibrillation in dogs by the use of magnesium sulfate in conjunction with the mercurial diuretic. Disturbances in conduction were unaffected. Anoxia of the cardiac muscle was found to intensify its sensitivity to the toxic action of mercury. Quinidine, instead of preventing ventricular fibrillation, appeared to precipitate it. Ventricular asystole has been reported to be the cause of death from an overdose of Mercuhydrin and ventricular fibrillation from Mercurophylline and Mersalyl.

The importance of the toxic cardiovascular reactions is apparent from reports of fatalities following intravenous injection of mercurial diuretics.[34] Death occurs quickly, usually within one to three minutes. The speed of injection is important in these reactions, as a rapid injection may "perfuse" the heart with a sufficiently high concentration of mercury to cause a fatal cardiac mechanism. With slow injection and adequate mixing with the blood, the concentration is relatively low. In some instances death followed the first injection; in others it came suddenly after many previous injections were well tolerated. Sometimes premonitory signs, such as apprehension, dyspnea, substernal discomfort, sweating, pallor, changes in pulse and giddiness, appeared with previous injections. A number of nonfatal convulsions have been reported. In addition to the immediate reactions, certain delayed reactions, such as fever, chills, asthmatic attacks and cutaneous eruptions, have been observed. The relatively large number of deaths which have occurred in children is impressive. The amount of mercury administered to children seems unusually large for the body weight.

Occasionally when some of the "warning signs" or a delayed reaction have been encountered, subsequent injections of a different mercurial diuretic have been well tolerated, but the presence of any reaction, either immediate or delayed, indicates the need for caution in the use of any additional mercurials. If necessity dictates their continued use, a small amount of a different preparation should be tried, preferably not by vein. If well tolerated, the amount may be increased.

There are no significant differences in toxicity among the commonly used mercurial diuretics, Mercuzanthin, Salyrgan and Mercuhydrin, all of which contain theophylline, but differences in reaction at the site of injection may occur when administration is intramuscular or subcutaneous. The feasibility of reducing the cardiotoxic properties of a mercurial diuretic while retaining the diuretic properties has been demonstrated by the use of monothiol compounds in conjunction with mercury. Thiomerin, in which sodium mercaptoacetate replaces the theophylline, is the latest mercurial diuretic to be introduced. Its diuretic potency is approximately equal to that of other diuretics but the cardiotoxic action and local reaction at the site of injection are minimal.[35] However, some toxic effects other than the acute cardiovascular reactions have been found to be more severe with this drug than with the other organic mercurial diuretics. In regard to delayed deaths occurring from five minutes to seven days after injection, Capps and associates[36] found Thiomerin to be more toxic in rats than Mercuhydrin or Mercurophylline by both intravenous and subcutaneous routes of administration. Observation over a period of four days after injection of Thiomerin into mice revealed delayed toxicity equal to that associated with Mercuhydrin, Mercuzanthin and Salyrgan. Thiomerin produced a greater decline in rate of glomerular filtration in dogs than did the other mercurials.[37] Stomatitis and diarrhea occurred more frequently among the dogs injected with Thiomerin. Although many enthusiastic reports have appeared about the low toxicity of Thiomerin, it must be remembered that it is a new drug and certain observations in animals indicate that further clinical observations concerning its toxicity are needed.

Clinical Applications

The specific indication for mercurial diuretics is well defined—the need for reduction in size of the extracellular fluid compartment and its maintenance at a desirable level. There are a number of clinical states in which this is desirable, such as congestive heart failure, the nephrotic syndrome and hepatic cirrhosis with ascites. Other clinical states associated with accumulation of fluids in the body, such as lymphedema, malignancy with ascites, and inflammatory states, do not usually respond favorably to mercurial diuretics. Although a reduction in edema may not be concerned with a direct attack upon the primary disease, the patient appears to be improved in most instances.

Studies on the relative efficacy of the various diuretics available commercially are too numerous to cite. As far as volume of diuresis is concerned, there is no particular advantage of one over the other by the intravenous route. Thiomerin, given subcutaneously, produces diuresis approximately equal to that resulting from intramuscular or intravenous injections of the other preparations. A drug which may be administered subcutaneously instead of intramuscularly or intravenously has definite advantages clinically: for example, it is less likely to produce reactions and may be administered by nurses, members of the family or the patient himself. This is particularly important in management of a severe illness like congestive heart failure in which climatic conditions and other factors may make office visits by the patient inadvisable.

The dosage of a mercurial diuretic varies widely, the ideal being the smallest amount which will produce satisfactory diuresis. In some subjects 2 cc. may be required whereas in others 0.5 cc. may be adequate. The amount used and the frequency of injection have varied considerably in the past. More recently, it has been popular to administer 2 cc. daily in the initial therapy of congestive heart failure. Such a vigorous regimen is usually unnecessary and is frequently unwise. The likelihood of

accumulation of mercury has already been discussed, but more serious are disturbances in electrolyte and water balance which may result from excessive diuresis. If bed rest, administration of oxygen, digitalis and morphine produce the desired effects, then mercury is unnecessary. The amount of mercury which will cause a daily loss of 2 to 3 pounds in the edematous patient is adequate and is indicated only if the other usual procedures fail. Frequency of injections must be dictated by the condition of the patient and his response to previous therapy. The rate of reduction in extracellular fluid should be determined by the clinical state of the patient. This type of therapy is symptomatic, and after the symptoms and signs due to accumulation of extracellular fluid have disappeared, nothing is accomplished by forcing additional diuresis to the point of diminished response. There is, however, considerable danger in depletion of electrolytes and water. Once a relatively asymptomatic state is reached, maintenance at that level should be attempted.

The maintenance dosage of mercury is entirely a matter of trial and error. Generally, smaller, more frequent amounts, such as 1 cc. twice weekly, are more preferable than larger amounts at less frequent intervals. It is much more desirable to maintain the weight below that level at which symptoms appear than to allow an accumulation of fluid and then produce vigorous diuresis with frequent large doses. Even when a maintenance dose is thought to have been established for the individual, it is likely to require alteration. The patient may establish a satisfactory state of compensation so that with reduced salt intake no mercury is necessary. On the other hand, when salt intake is increased either by intention or by accident, the maintenance dose of the mercurial diuretic must often be increased. The onset of disturbances in cardiac mechanism and the occurrence of infections, particularly of the upper respiratory tract, frequently necessitate an increase in the maintenance dose.

Administration by the intravenous and intramuscular routes has been the method of choice because the routes are more dependable. Suppositories containing a mercurial diuretic have been tried but local irritation and unpredictable absorption make this route impractical.

Oral administration of mercurial diuretics has been investigated and the unpredictable absorption by this route has been previously indicated. An average of approximately 1 to 3 per cent of the mercury administered by mouth appears in the urine, the range being 0 to 12 per cent. The oral route is unsatisfactory for early therapy in severe congestive heart failure because the diuretic potency by this route is limited. In addition, the amount necessary to institute diuresis often produces nausea, vomiting and diarrhea. This route may be of benefit in maintenance after initial diuresis has been accomplished by the parenteral route. Even though only a small amount is absorbed from the gastrointestinal tract, the frequent small amounts may be sufficient to prevent formation of edema. The ease of administration by this route, obviating visits to an office or an outpatient department, makes it desirable.

It has been suggested by Olson[38] that 0.25 to 0.33 cc. of Thiomerin administered subcutaneously daily by the patient or a relative may be effective, economical and simpler. Although there may be no apparent diuresis from these small amounts, the subtle changes produced by frequent injections maintain desired weight levels satisfactorily. In patients severely decompensated, large doses may be found necessary to produce the desired effects. This can be determined readily by clinical trial. In some instances, daily administration of the diuretic at home by the subcutaneous route may permit the patient to ingest small quantities of sodium whenever he finds a low salt diet difficult to accept.

Considerable attention has been given to the "low salt syndrome." This usually results from too frequent and injudicious use of mercurial diuretics and is characterized by weakness, apathy, anorexia, vomiting, mental confusion and coma. In addition there may be depression of urinary volume and chlorides, decreased sodium and chloride concentration in the serum, and azotemia. It is often mani-

fested by failure to respond to mercurials. Response to mercurial diuretics is known to be diminished when the concentration of sodium or chloride in the serum is low. The low salt syndrome may be corrected with hypertonic solutions of sodium chloride.

Ammonium chloride increases the diuretic response to mercurials 15 to 25 per cent in normal subjects. When the concentration of chlorides in the serum is low and the response to mercury is poor or absent, administration of ammonium or calcium chloride with restoration of the normal concentration of chlorides in the serum will increase diuresis several fold. Usually ammonium chloride is not necessary, as mercury alone will suffice, but if the individual is subjected to frequent mercurial diuresis, the concentration of chlorides in the serum is likely to be low, and ammonium chloride is indicated.

Other measures which may increase the diuretic response to mercury, apparently by increasing the rate of glomerular filtration, include aminophylline or theophylline, 0.5 Gm. given intravenously with the mercurial diuretic. Rest in bed is important for the patient with severe congestive failure[39] since it may improve renal blood flow. Phlebotomy, with removal of 500 to 750 cc. of blood just prior to the injection of mercury, may result in good diuresis when mercurials have failed previously. Disturbances in electrolytes or renal failure are most commonly responsible for unsatisfactory response to mercurials. As previously stated, the electrolyte state should be corrected and then mercurial diuretics may be tried again.

The use of mercurial diuretics in congestive heart failure will shorten the time required to ameliorate certain aspects of the clinical syndrome. However, clinicians are too often erroneously guided by the time factor rather than by the underlying fundamental cardiac state. Disappearance of edema or most of the symptoms of failure does not indicate complete restoration of cardiac reserve. Mercurial diuretics are not substitutes for digitalis nor are they specific agents which cure cardiac disease. When employed properly, they are useful and when employed carelessly, harmful.

Contraindications

Acute renal disease, such as acute glomerulonephritis, and chronic renal disease with insufficiency are contraindications to the use of mercurial diuretics. It is often difficult to evaluate elevated blood urea nitrogen, albuminuria and hematuria in the presence of congestive heart failure, since they may be present in the absence of any primary renal disease. However, if the blood urea nitrogen exceeds 60 mg. per 100 cc., mercurial diuretics should be used extremely cautiously if at all. The appearance of definite albuminuria, hematuria or oliguria after administration of a mercurial diuretic when they were previously absent is indication for discontinuation of the drug.

One of the most frequently encountered contraindications to the use of mercurial diuretics is failure of response to previous injections. Further use of diuretics should not be attempted until possible electrolyte disturbances have been corrected or until a careful evaluation of the clinical state, including the kidneys, has been made. Further use of mercurials should be undertaken cautiously.

The occurrence of any of the immediate reactions to an intravenous injection of a mercurial diuretic contraindicates further use of this route if mercury has to be given at all. Occasionally, a change in the preparation and in the route of administration may be tolerated. The immediate reactions which may serve as premonitory signs are tachycardia, faintness, pallor, sweatiness and asthmatic episodes. Delayed reactions of fever, chills and cutaneous rashes may also be regarded as warning signs.

Tetany may result from excessive loss of calcium during diuresis. This should be corrected before additional mercury is given. Digitalis intoxication may be precipitated by excessive diuresis. Further use of mercurials should be avoided until the excess of digitalis has been excreted.

Minor reactions, such as cramps in the legs, suggest the need for a smaller dose of the diuretic or possibly less frequent injections but do not contraindicate its continued use. Severe, dangerous reactions almost invariably follow intravenous administration; therefore,

the intramuscular or subcutaneous route should be employed routinely. The intravenous route should be reserved only for absolutely necessary circumstances, such as severe edema and failure, in which impairment of blood flow and absorption may prevent therapeutic responses. Except for the brief statement of Batterman,[39] only one report of a fatal case[40] could be found in which the drug was administered intramuscularly or subcutaneously.

REFERENCES

[1] Thomson, W. A. R.: The organic mercurial diuretics in the treatment of cardiac oedema. Quart. J. Med. **6:** 321, 1937.

[2] Saxl, P., and Heilig, R.: Ueber die diuretische Wirkung von Novasurol und anderen Quecksilberinjektionen. Wien. klin. Wchnschr. **33:** 943, 1920.

[3] Sollman, T.: A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology, ed. 6. Philadelphia, W. B. Saunders, 1942.

[4] Taylor, F. H. L., and Young, A. G.: Biochemical studies of mercury compounds. Effect of acids, bases, salts and blood serum on diffusion of mercury compounds in vitro. J. Pharmacol. & Exper. Therap. **38:** 217, 1930.

[5] Earle, D. P., Jr., and Berliner, R. W.: Effect of 2,3-dimercaptopropanol on diuresis. Am. J. Physiol. **151:** 215, 1947.

[6] Sollman, T., and Schreiber, N. E.: Comparative diuretic response to clinical injections of various mercurials. Arch. Int. Med. **58:** 1067, 1936.

[7] Kolmer, J. A.: Principles and Practice of Chemotherapy. With Special Reference to the Specific and General Treatment of Syphilis. Philadelphia, W. B. Saunders Co., 1926.

[8] Brightman, I. J., and Lehman, R. A.: Experimental study of rectal administration of mercurial diuretics. J. Lab. & Clin. Med. **25:** 56, 1939.

[9] Overman, W. J., Gordon, W. H., Jr., and Burch, G. E.: Tracer studies of the urinary excretion of radioactive mercury following oral administration of a mercurial diuretic. Circulation **1:** 496, 1950.

[10] DeGraff, A. C., Batterman, R. C., and Lehman, R. A.: Influence of theophylline upon absorption of mercupurin and salyrgan from site of intramuscular injection. J. Pharmacol. & Exper. Therap. **62:** 26, 1938.

[11] Lehman, R. A., and King, E. E.: Pharmacology of thiomerin. Federation Proc. **8:** 314, 1949.

[12] Kelly, F. J., Svedberg, A. H., and Harp, V. C., Jr.: The transfer of radioactive mercury across a membrane produced by the application of cantharides to the skin of man. J. Clin. Investigation **29:** 988, 1950.

[13] Lomholt, S.: Absorption and elimination of mercury in the different methods used in the treatment of syphilis. Brit. J. Dermat. & Syph. **32:** 353, 1920.

[14] Huffman, E. R.: Mercury excretion following oral mercurial diuretics in man. Am. J. Med. **6:** 663, 1949.

[15] Burch, G. E., Threefoot, S. A., Ray, C. T., and Kelly, F. J.: The distribution of radiomercury of a mercurial diuretic in some of the body fluids of man. Am. J. M. Sc. **220:** 160, 1950.

[16] Burch, G., Ray, T., Threefoot, S., Kelly, F., and Svedberg, A. H.: The urinary excretion and biologic decay period of radiomercury labeling a mercurial diuretic in normal and diseased man. J. Clin. Investigation. **29:** 1131, 1950.

[17] Milnor, P., Burch, G., Ray, T., Threefoot, S., and Berenson, G.: Considerations of renal, hepatic and extremital arteriovenous differences in concentration of radiomercury of a mercurial diuretic. J. Clin. Investigation **24:** 72, 1950.

[18] Bartram, A.: Experimental observations on effect of various diuretics when injected directly into one renal artery of dog. J. Clin. Investigation **11:** 1197, 1932.

[19] Govaerts, P.: Origine rénale ou tissulaire de la diurèse par un composé mercuriel organique. Compt. rend. Soc. de biol. **99:** 647, 1928.

[20] Richards, A. N.: Direct observations of change in function of renal tubule caused by certain poisons. Tr. A. Am. Physicians **44:** 64, 1929.

[21] Weston, R. E., Grossman, J., Edelman, I. S., Escher, D. J. W., Leiter, L., and Hellman, L.: Renal tubular action of diuretics. II. Effects of mercurial diuresis on glucose reabsorption. Federation Proc. **8:** 164, 1949.

[22] Berliner, R. W., Kennedy, T. J., Jr., and Hilton, J. G.: Salyrgan and renal tubular secretion of para-aminohippurate in the dog and man. Am. J. Physiol. **154:** 537, 1948.

[23] Duggan, J. J., and Pitts, R. F.: Studies on diuretics. I. The site of action of mercurial diuretics. J. Clin. Investigation **29:** 365, 1950.

[24] Pitts, R. F., and Duggan, J. J.: Studies on diuretics. II. The relationship between glomerular filtration rate, proximal tubular absorption of sodium and diuretic efficacy of mercurials. J. Clin. Investigation **29:** 372, 1950.

[25] Blumgart, H. L., Gilligan, D. R., Levy, R. C., Brown, M. G., and Volk, M. C.: Action of diuretic drugs. Action of diuretics in normal persons. Arch. Int. Med. **54:** 40, 1934.

[26] Keith, N. M., and Whelan, M.: A study of the action of ammonium chloride and organic mercury compounds. J. Clin. Investigation **3:** 149, 1926.

[27] Schwartz, W. B., and Wallace, W. M.: Observations on electrolyte balance during mercurial diuresis in congestive heart failure. Abstracts,

42nd Annual Meeting of Am. Soc. Clin. Investigation, 1950. P. 54.

[28] FARAH, A., AND MARESH, G.: Influence of sulfhydryl compounds on diuresis and renal and cardiac circulatory changes caused by mersalyl. J. Pharmacol. & Exper. Therap. **92:** 73, 1948.

[29] BURMEISTER, W. H., AND MCNALLY, W. D.: Acute mercury poisoning. J. M. Res. **36:** 87, 1917.

[30] LIPPMAN, R. W.: Effect of proteinuria on toxicity of mercurial diuretics in the rat. Proc. Soc. Exper. Biol. & Med. **72:** 682, 1949.

[31] JOHNSTON, R. L.: Cardiac depression by mercurial diuretics. J. Lab. & Clin. Med. **27:** 303, 1941.

[32] LONG, W. K., AND FARAH, A. E.: Influence of certain sulfhydryl compounds on toxicity of organic mercurial diuretic. J. Pharmacol. & Exper. Therap. **88:** 388, 1946.

[33] PINES, I., SANABRIA, A., AND HERNANDEZ ARRIENS, R. T.: Mercurial diuretics. The addition of magnesium sulfate to prevent the toxic effects of their intravenous administration. Brit. Heart J. **6:** 197, 1944.

[34] KAUFMAN, R. E.: Immediate fatalities after intravenous mercurial diuretics. Ann. Int. Med. **28:** 1040, 1948.

[35] BATTERMAN, R. C., UNTERMAN, D., AND DEGRAFF, A. C.: The subcutaneous administration of mercaptomerin (thiomerin). J. A. M. A. **140:** 1268, 1949.

[36] CAPPS, R. T., KOZELKA, F. L., AND ORTH, O. S.: Chronic toxicity of thiomerin compared to other mercurial diuretics. Proc. Soc. Exper. Biol. & Med. **74:** 511, 1950.

[37] HANDLEY, C. A., SIGAFOOS, R. B., TELFORD, J., AND LA FORGE, M.: Effect of chronic administration of mercurial diuretics on glomerular filtration in the dog. Proc. Soc. Exper. Biol. & Med. **72:** 201, 1949.

[38] OLSON, J. G.: Personal communication.

[39] BATTERMAN, R. C.: The treatment of congestive heart failure with mercurial diuretics. M. Clin. North America p. 629, 1950.

[40] WALLNER, A., AND HERMAN, L.: Mercurial diuretics: Some hazards of mercuhydrin. Report of two cases with one death. Ann. Int. Med. **32:** 1190, 1950.

ABSTRACTS

BACTERIAL ENDOCARDITIS

Petersen, E. S., McCullough, N. B., Eisele, C. W., and Goldinger, J. M.: Subacute Bacterial Endocarditis Due to Streptobacillus Moniliformis. J. A. M. A. **144:** 621 (Oct.), 1950.

Five previous cases of bacterial endocarditis due to *Streptobacillus moniliformis* are known and 4 have been reported in the literature. All these cases ended fatally. Three were in the penicillin era, two occurred soon after the use of penicillin but before massive doses of the drug were used. The authors report the following case because it is an apparent cure, and possibly the first one having this infecting organism. The patient, a 40 year old male, had rheumatic fever at age 14 with a recurrence at 16, at which time a heart murmur was noted. He entered many cellars and warehouses infested with rats in his work as a real estate appraiser. He recalled no rat bite or direct contact with a rat or other animal. On June 11, 1948, he first noticed fever; on June 18, a blood culture was taken and he was admitted to the hospital. During his hospital stay eight venous and one arterial blood culture were taken; all were positive for *S. moniliformis*. After sensitivity tests were run penicillin was selected for treatment. This was given over a period of 47 days in dosages increasing from one million to two million units daily. Blood levels rose from one unit per cc. to 8 units per cc. in the final phases of treatment. This treatment resulted in an apparent cure with no recurrence for a month after discharge.

KITCHELL

Matlage, W. T., Harrison, P. E., and Greene, J. A.: Neisseria Flava Endocarditis. Ann. Int. Med. **33:** 1494 (Dec.), 1950.

The authors report the case of a 14 year old Mexican female who presented the typical clinical features of pelvic peritonitis and generalized sepsis. After repeated attempts to culture an organism from the blood stream, a positive blood culture of neisseria was obtained. The cultural characteristics suggested that the organism was either a variant of *Neisseria gonorrhea* or an example of the *Neisseria flava* species. Recovery occurred after massive doses of penicillin and sulfonamides were administered. When evidences of sepsis were most pronounced, a blowing systolic precordial murmur, unaccompanied by thrill, diastolic murmur or cardiac enlargement, was audible. Following recovery, the murmur became indistinct. It is therefore suggested that this case may have been one of the rare instances of *Neisseria flava* septicemia complicated by an endocarditis due to this organism.

WENDKOS

BLOOD COAGULATION

Alexander, B., Goldstein, R., and Landwehr, G.: The Prothrombin Conversion Accelerator of Serum (SPCA): Its Partial Purification and its Properties Compared with Serum Ac-Globulin. J. Clin. Investigation **29:** 881 (July), 1950.

The authors studied serum Ac-globulin and the serum prothrombin conversion accelerator in an attempt to determine any possible relationship be-

tween the two substances. According to other workers, prothrombin conversion accelerator accelerates the conversion of prothrombin to thrombin in the presence of a plasma component which is labile. Ac-globulin has been found to have similar physiologic properties.

Several differences were noted in the reactions of the two substances. The authors attempted to explain them away, however, by postulating that serum Ac-globulin comprises a mixture, or perhaps a chemical combination of at least two important clotting components, plasma Ac-globulin, a labile constituent of plasma, and prothrombin conversion accelerator.

ABRAMSON

Warren, R., Amdur, M. O., Belko, J., and Baker, D. V.: Postoperative Alterations in the Coagulation Mechanism of the Blood: Observations on Circulating Thromboplastin. Arch. Surg. **61:** 419 (Sept.), 1950.

The authors studied the changes in plasma protein, platelets, plasma fibrinogen and plasma thromboplastin following a surgical operation. A slight but insignificant fall in the prothrombin activity of whole plasma was observed from the first to the seventh postoperative day, a similar change being noted in the serum prothrombin between the first and fourth days. The platelet count fell on the second, third and fourth days, followed by a rise on the tenth to the thirteenth days, while a rise in plasma fibrinogen concentration occurred between the third and ninth days.

The cause for the fall in plasma prothrombin is obscure, although the possibility that it is due to transient injury to the liver during the operative period must be considered. The reason for the early fall and the later rise of platelets is also not clear. The rise in fibrinogen in the early postoperative period is probably a manifestation of the fibrinogen response as a nonspecific reaction of the body to trauma, toxic states or infection. The fall in serum prothrombin in the early postoperative period can be considered as evidence suggestive of the presence of circulating free thromboplastin during this time. The source of this material may be tissue juices from the operative site, reaching the blood stream through the lymphatic vessels, or, possibly, from the destruction of platelets.

ABRAMSON

Quick, A. J.: A New Concept of Venous Thrombosis. Surg., Gynec. & Obst. **91:** 296 (Sept.), 1950.

In the production of a clot, thrombin, once formed as a result of the interaction of the prothrombin complex with thromboplastin, enzymically converts fibrinogen to fibrin and at the same time acts on the platelets, making them labile so that they readily disintegrate. As a result of the latter reaction, activator is liberated and then more thromboplastinogen is converted to the reactive state. This in turn causes the production of more thrombin. What prevents such a chain reaction from converting all the circulating blood into a solid clot is the fact that thrombin is promptly removed by adsorption to the enormous surface of the fibrin reticulum in the clot.

Even minor changes may alter the physiochemical behavior of the endothelial surface of a vessel and destroy the normal ability of this tissue to prevent the adherence of platelets. When agglutination of platelets occurs, lysis follows and, as a result, thrombin and subsequently a reticulum of fibrin are formed. As the initial clot undergoes retraction, a serum rich in nascent thrombin is expressed. If the circulation is rapid, this material is washed away and the thrombus fails to propagate. If it is sluggish, the extruded serum causes the clotting of blood about the thrombus and a new clot is built on the old one. The latter retracts and thus brings about conditions conducive to further growth of the thrombus.

Clot retraction is, therefore, an important factor in the propagation of a clot, since it supplies a source of thrombin. The reaction is influenced first by the number of circulating platelets, second, by the speed and quantity of thrombin production, and finally, by the cell volume. The greater the number of cells, the bigger is the bulk of the nonretractile part of the clot and hence the less serum, rich in thrombin, is expressed. This may help to explain why anemia, associated with a greater retractility of the clot, appears to predispose to thromboembolism.

ABRAMSON

Butler, B. C., Taylor, H. C., Sr., and Graff, S.: Relationship of Disorders of the Blood-Clotting Mechanism to Toxemia of Pregnancy and the Value of Heparin in Therapy. Am. J. Obst. & Gynec. **60:** 564 (Sept.), 1950.

The authors administered heparin to 4 patients with toxemia of pregnancy to test the thromboplastin theory of toxemia. According to this view, a placental toxin (thromboplastin) is produced. Heparin would therefore be expected to produce a therapeutic response in the condition, since in proper amounts it may prevent the action of thromboplastin. However, heparin was not found to be an effective therapeutic agent in the reported cases. The authors interpreted this data as being strong evidence against the thromboplastin theory of toxemia in pregnancy.

ABRAMSON

Conley, C. L., Ratnoff, O. D., Ellicott, C. E., and Hartmann, R. C.: Studies on the Initiation of Blood Coagulation. II. An Anticoagulant Inhibiting the Activation of a Plasma Thromboplastic Factor. J. Clin. Investigation **29:** 1182 (Sept.), 1950.

A 37 year old woman with a persistent hemor-

rhagic diathesis was found to contain an unusual anticoagulant in her plasma. This substance inhibited the coagulation of normal blood. It did not inhibit thrombin, prothrombin, or accelerator globulin, thromboplastin, or platelet activity. Evidence is presented which suggests that the anticoagulant prevented the appearance of thromboplastic activity in shed blood, since it appears that platelet-free plasma contains a potentially thromboplastic substance.

WAIFE

Quick, A. J., and Hussey, C. V.: The Mechanism of Clot Retraction. Science **112**: 558 (Nov.), 1950.

Clot retraction occurs only when fresh, intact platelets, thrombin, and fibrinogen are simultaneously present. In these experiments the concentration of thrombin and fibrinogen was varied. It was found that, in vitro, the higher the number of platelets and the greater the concentration of thrombin in relation to fibrinogen, the more complete will be the retraction of the clot. Platelets in the absence of thrombin remain discrete and do not adhere to foreign surfaces. In the presence of thrombin, platelets are altered so that they become sticky and agglutinate. Thrombin also coats fibrin strands so that platelets, in contact with this surface, adhere and undergo physicochemical changes which apparently cause shortening and contraction of the fibrin reticulum.

WAIFE

CONGENITAL ANOMALIES

Marcondes, J. R., Teixeira, O., Santos, A., Martirani, A., Mattar, G., and Montenegro, M. R.: Complete Transposition of the Great Vessels Associated with a Single Ventricle, Interatrial Septal Defect, and Mitral Atresia. Arq. brasil. cardiol. **3**: 329 (June), 1950.

The authors report the case of a 3 year old cyanotic child with an unusual combination of multiple congenital malformations of the heart, consisting of transposition of the great vessels, cor biatriatum triloculare, interatrial septal defect, pulmonary stenosis, and mitral atresia. Roentgenologic examination showed an enlarged heart with a convexity in the region of the pulmonary conus, in addition to decreased hilar markings. The patient died of congestive heart failure. Necropsy revealed the cardiac defects and an abnormal position of the abdominal organs with an acute gastric ulcer due to thrombosis of the arteries of the greater curvature of the stomach. A discussion of differential diagnosis is presented with a detailed analysis of the angiocardiogram which, according to the authors, is the first such examination reported of this rare type of congenital heart disease.

SCHLESINGER

Ordway, N. K., Levy, L., II., Hyman, A. L., and Bagnetto, R. L.: Pulmonary Stenosis with Patent Foramen Ovale. Am. Heart J. **40**: 271 (Aug.), 1950.

The authors present the case history of a 22 year old man with pulmonary stenosis and patent foramen ovale. During heart catheterization when the tip of the catheter passed into the pulmonary artery, the blood oxygen content changed considerably. On the basis of these changes, the authors estimated (a) the diameter of the pulmonary valve orifice was from 2.5 to 6.25 mm., (b) intracardiac right to left shunt was 68 per cent to 93 per cent of the systemic blood flow, and (c) precapillary left to right shunt in the lungs was up to 36 per cent of the systemic blood flow. Autopsy examination later revealed right ventricular hypertrophy, patent foramen ovale, and fusion of the pulmonary valve cusps resulting in a diaphragm with a 2.5 mm. central opening. Since the diameter of the cardiac catheter was the same as the pulmonary valve orifice, it is likely that little blood could have passed around the catheter during life. To differentiate patients with pulmonary stenosis and patent foramen ovale from those with tetralogy of Fallot, the authors stress the importance of (1) the long delay of contrast medium in the dilated right ventricle and the concomitant poor visualization of the aorta to rule out overriding aorta and patent ventricular septal defect, and (2) the disparity between right ventricular and systemic systolic pressures. The latter values approximate each other in the tetralogy of Fallot.

HELLERSTEIN

Potts, W. J., Gibson, S., Riker, W. L., and Leininger, C. R.: Congenital Pulmonary Stenosis with Intact Ventricular Septum. J.A.M.A. **144**: 8 (Sept.), 1950.

The authors report 4 cases of pulmonary valvulotomy on patients ranging in age from 23 days to 10½ years. The authors devised a valvulotome which decreases the size of the wound of the heart and lessens hemorrhage and arrhythmia. A curved subpectoral incision was made and the chest was opened through the third left intercostal space. A tiny incision was made in the pericardial sac and 1 per cent procaine was introduced and allowed to bathe the heart to prevent arrhythmia and irritability. The valvulotome is thrust through the wall of the ventricle at a very acute angle. As soon as the stenotic veil over the pulmonary valve was cut increased pressure in the pulmonary artery was easily discernible to the palpating finger. Prophylactic penicillin was used twice daily for five to seven days. The results were spectacular in all cases and the authors feel that transventricular incision of such pulmonary stenoses is a sound procedure.

KITCHELL

Ruskin, H. and Samuel, E.: Calcification in the

Patent Ductus Arteriosus. Brit. J. Radiol. **23**: 710 (Dec.), 1950.

The authors describe four instances in which calcification within the walls of a patent ductus arteriosus was demonstrated. Demonstration of a curvilinear calcification between the pulmonary artery and the aorta with its concavity directed upwards and to the right in the posterior-anterior position suggests the diagnosis. The site of the calcification was confirmed in the left anterior oblique position. Technically, both the method of overpenetration and that of tomography were considered satisfactory.

SCHWEDEL

Weissel, W.: Unipolar Electrocardiography in Congenital Anomalies of the Heart. Cardiologia **16**: 191, 1950.

The author examined 26 cases of congenital heart disease with unipolar lead electrocardiography. Electrocardiograms were obtained from 12 different points of the right and left chest and from the extremities. The tracings obtained in different lesions are described. The value of this examination method for the location of the position of the ventricles and for the estimation of the degree of the rotation of the heart is stressed. Unipolar electrocardiograms obtained from the right and left chest were particularly valuable in the diagnosis of dextrocardias without total situs inversus.

Runström, G., and Sigroth, K.: Two Cases of Vascular Anomalies in the Lung. Acta Med. Scandinav. Suppl. **246**: 176, 1950.

The authors point out that arteriovenous aneurysms are the most common and important vascular malformations of the lung.

A man aged 26 years with a pulmonary arteriovenous aneurysm is described. He had hereditary hemorrhagic telangiectasia. A continuous interscapular murmur was audible during examination of the left lung. The diagnosis was confirmed by catherization and angiocardiography with the injection of 65 ml. of 70 per cent Diodrast through a catheter inserted into the left main branch of the pulmonary artery. An aneurysm resembling a bunch of grapes was outlined with filling of two large veins before any contrast medium appeared in other parts of the lung. In connection with this angiographic examination the patient had hemoptysis and apnea lasting two to three minutes. The aneurysm was removed by lobectomy.

The second case was a man aged 21 years with an anomalous drainage of a pulmonary vein into the inferior vena cava. This diagnosis was made from unusual vascular patterns observed in roentgen studies of the thorax.

The authors recommend cerebral angiography in all cases of vascular malformations of the lung connected with neurologic symptoms in order to exclude cerebral vascular malformations. Roentgen examination of the chest is suggested when a cerebral vascular anomaly is found.

ROSENBAUM

CONGESTIVE HEART FAILURE

Sinclair-Smith, B. C., Sissow, J., Kattus, A. A., Genecin, A., Monge, C., McKeever, W. and Newman, E. V.: The Effects of Posterior Pituitary Extract and Smoking on Water, Sodium and Chloride Excretion in Normal Subjects and in Patients with Congestive Heart Failure. Bull. Johns Hopkins Hosp. **87**: 221 (Sept.), 1950.

The authors studied the effects of the intravenous administration of Pitressin in 3 normal controls and in 3 patients in congestive heart failure, and the effect of smoking in normal subjects on the glomerular filtration rate and the urinary excretion of sodium chloride and water. Although there was a consistent antidiuresis in all instances, there was no change in the glomerular filtration rate and no change in the rate of sodium and chloride excretion in either the normal group or in those with congestive heart failure. The antidiuretic effect of mild exercise is probably due to posterior pituitary action; however, there is also a reduction in sodium chloride excretion without any change in the glomerular filtration rate. This is interpreted as being due to different physiologic mechanisms, probably of adrenal cortical nature. The authors conclude that it is unlikely that the accumulation of edema fluid in congestive heart failure is caused by the action of the posterior pituitary on the renal tubule as sodium chloride retention does not occur with the administration of small doses of Pitressin.

MARGOLIES

De Vries, A., Fryd, H. H., Jetelson, S. and Herz, N.: Repeated Bleeding in a Case of Cor Pulmonale. Cardiologia **16**: 169, 1950.

The authors treated a case of chronic cor pulmonale with congestive heart failure by repeated bleeding, after digitalis therapy and mercurial diuretics proved unsuccessful. The drawing of a total of 1330 cc. of blood within a period of three days lowered the elevated venous pressure and increased the cardiac output, as indicated by a rise in pulse pressure and a marked diuresis. If bleeding was then continued, the venous pressure fell further, but the pulse pressure remained unchanged. This is in accord with Starling's law, since a rise in cardiac output, reflected in the pulse pressure, is expected to occur only if the venous pressure is lowered from initially high values.

The authors recommend repeated bleeding as the treatment of choice "in that phase of heart failure in chronic cor pulmonale, which is characterized by a high hematocrit and a marked increase of circulating blood volume."

PICK

CORONARY ARTERY DISEASE, MYOCARDIAL INFARCTION

Bustamante, R., Perez Stable, E., Guerra, R., and Milanes, B.: Visualization of the Coronary Arteries in Man. Arch. Inst. cardiol. México **20:** 350 (June), 1950.

The authors report experiments on patients using Radner's method for visualization of the coronary arteries. A catheter was introduced through the brachial artery into the ascending aorta under fluoroscopic control. Then, 50 cc. of a 70 per cent solution of Diodrast were injected under high pressure. Thirteen clinical cases were studied. Satisfactory results were obtained in 8 patients. No accidents or disturbances are reported.

LUISADA

Hauss, W. H. and Koppermann, E.: The Minute Volume in Myocardial Infarction. Ztschr. f. Kreislaufforsch. **39:** 449 (Aug.), 1950.

The authors used the method of Wezler and Boeger for a study of the dynamics of the circulation in 9 patients with various stages of myocardial infarction. Cardiac output (stroke and minute volume) decreased immediately following the attack and the arterial pressure was maintained during this time by a rise of peripheral resistance. This change in the dynamics of the circulation lessens the work of the heart and thus represents a protective mechanism for the injured myocardium. Normal conditions of circulation are reestablished slowly within the following weeks and are associated with signs of clinical improvement.

PICK

Blache, J. O., and Handler, F. P.: Coronary Artery Disease: A Comparison of the Rates and Patterns of Development of Coronary Arteriosclerosis in the Negro and White Races with Its Relation to Clinical Coronary Artery Disease. Arch. Path. **50:** 189 (Aug.), 1950.

The authors add the results of their investigation to a controversial subject, namely, the comparative incidence of coronary arteriosclerosis in the Negro and white races. Their conclusion agrees with the majority opinion that the white patient at similar age level shows more coronary artery disease, and is more likely to develop coronary thrombosis, than the Negro. They studied microscopically and by microincineration the first two centimeters of the anterior descending branch of the left coronary artery in consecutive autopsies. The authors assert that the development of coronary arteriosclerosis in the Negro lags behind that of white subjects by a decade, especially notable in middle age. In old age, the difference is slight. There is less calcification of the thickened intima and in the media of Negro patients. This, in the investigators' opinion, is significant, since it is believed that calcification precedes and conditions the formation of intimal plaques. They also noted an interesting anatomic feature, possibly contributory—the high position of the coronary ostia in Negroes (frequently above the line of closure of the aortic valve cusps).

GOULEY

Livingstone, D. J.: Acute Myocardial Infarction following Tetraethylammonium Chloride Therapy. Brit. M. J. **2:** 713 (Sept.), 1950.

The author reports 3 cases of occlusive arteriosclerosis of the lower limbs in which tetraethylammonium therapy was followed by acute myocardial infarction. Two were proved posterior infarcts and in one clinical confirmation was made without an electrocardiogram. All presented evidence of arteriosclerosis. The author warns of the danger of using this drug, particularly in the presence of arteriosclerosis, even in the absence of hypertension or marked cardiac symptoms.

TANDOWSKY

Eckstein, R. W., Stroud, M., III, Eckel, R., Dowling, C. V., and Pretchard, W. H. Effects of Control of Cardiac Work upon Coronary Flow and Oxygen Consumption after Sympathetic Nerve Stimulation. Am. J. Physiol. **163:** 539 (Dec.), 1950.

The authors measured aortic pressures, cardiac output and work, coronary flow and myocardial oxygen consumption in dogs. Cardiac augmentor nerve stimulation produces an epinephrine-like effect in the myocardium which increases oxygen consumption and coronary blood flow in spite of marked experimental reduction of cardiac work by simultaneous inflation of balloons in superior and inferior venae cavae. Augmentor nerve stimulation produces cardiac anoxia and inefficiency by releasing an epinephrine-like substance. The authors state that "it is not justifiable to attribute changes in coronary flow to direct action of nerves or drugs upon coronary arteries unless myocardial metabolic requirements are controlled." It is pointed out that if myocardial oxygen use could be kept constant during augmentor stimulation (as by controlling work by reduction of venous inflow) the responses of the coronary arteries could be studied independently. These experiments do not serve to separate direct nerve effects from metabolic effects on coronary arteries.

OPPENHEIMER

Segers, M., and Brombart, M.: On a Case of Calcified Infarction. Acta Cardiol. **5:** 540, 1950.

The authors report a case of old calcified infarction in a 69 year old male. Three years after the acute episode, clinical examination was negative while the electrocardiogram revealed evidence of an old apical myocardial infarction; the x-ray showed the existence of a calcified area at the apex. At fluoroscopy, this area showed contractions of small amplitude but no evidence of systolic expansion.

The author reviews all causes of cardiac calcification and discusses the roentgenologic data for differential diagnosis between calcified pericarditis and calcified infarction.

LUISADA

ELECTROCARDIOGRAPHY

Schlesinger, P.: Difficulties in the Electrocardiographic Diagnosis of Right Ventricular Hypertrophy. Arq. Clin. **10:** 141 (April), 1950.

Following a brief review of the main criteria for the electrocardiographic diagnosis of right ventricular hypertrophy, the author analyzes certain instances in which this diagnosis may be difficult to assert by the usual standard and precordial leads. Counterclockwise rotation of the heart may deviate the transition zone far to the right of the precordium, so that the essentially positive deflections of the hypertrophied right ventricle appear not in lead V_1, but in leads V_{3R} and V_{4R}. A low position of the diaphragm, such as occurs in emphysema, requires the registration of additional leads at lower thoracic levels to elicit the typical electrocardiographic changes of right ventricular hypertrophy. Coexistent hypertrophy of the left ventricle is also an important factor in certain cases in which the tracing may show no signs of right ventricular hypertrophy. Complete and incomplete right bundle branch block are not uncommonly present and render the positive diagnosis of associated right ventricular hypertrophy extremely difficult from the electrocardiographic standpoint, since tall R waves occur in leads from the right side of the precordium in both instances. Finally, some patients with right ventricular hypertrophy show absent R waves in the right precordial leads. They correspond to those cases in which the atypical electrocardiogram is due to preponderant hypertrophy of certain portions of the right ventricle, such as to determine electrical forces of activation opposed in direction to the precordial electrode.

AUTHOR

Scherf, D., Morgenbesser, L. J., Nightingale, E. J., and Schaeffeler, K. T.: Mechanism of Ventricular Fibrillation. Cardiologia **16:** 232, 1950.

In experiments on dogs ventricular flutter and fibrillation were caused by topical application of aconitine on the surface of the ventricles. Ventricular flutter was invariably stopped by cooling the area on which aconitine had been applied. Cooling neither stopped nor modified ventricular fibrillation. Rapid stimulation of one ventricle of the dog causes repetitive discharges in the other ventricle. It is assumed that in ventricular flutter only one center forms rapid stimuli, while in ventricular fibrillation many centers are responsible for its production.

AUTHORS

Walz, L. Ruf, F., and Rosch, H.: Differential Diagnosis of the Electrocardiogram in Trauma of the Heart. Viewpoints Concerning the Effect of Pericarditis on the P-Q Interval and the Theory of Ventricular flutter. Ztschr. f. Kreislaufforsch. **39:** 216 (April), 1950.

The authors report their observations in limb lead electrocardiograms taken before, during, and following surgery on 6 patients with various direct injuries to the heart. An injury current (S-T deviation) due to direct trauma can be distinguished from an injury current due to infarction following traumatic involvement of a coronary artery. In the latter case, the S-T deviation persists for several days, while in the former case the change is transient and may be missed if examination of the patient is delayed. An approximate localization of the point of injury can be obtained by determination of the direction of the vector of the injury current, constructed in an Einthoven triangle. Depression of the P-Q segment can be seen following surgical manipulation of the basal parts of the heart, and is attributed by the authors to atrial pericarditis.

Ventricular beats and runs of ventricular tachycardia and flutter are explained by mechanical irritation of the myocardium during operations on the heart. The varying contour in the electrocardiogram associated with the ectopic beats supports, in the opinion of the authors, the theory of a multifocal origin of ventricular flutter.

PICK

Barnett, A. J., Blacket, R. B., Depoorter, A. E., Sanderson, P. H., and Wilson, G. M.: The Action of Noradrenaline in Man and its Relation to Phaeochromocytoma and Hypertension. Clin. Sc. **9:** 151 (May), 1950.

The authors studied the effect of intravenous administration of noradrenaline and adrenaline in normal subjects. In all instances noradrenaline produced a steady rise in systolic and diastolic blood pressure and a coincident slowing of the heart. With adrenaline, however, there was first a conspicuous but fleeting fall in both levels of pressure and a considerable cardiac acceleration. These changes were followed by a rise in systolic pressure to a level above the initial pressure and a rise in diastolic pressure to about its previous height. Noradrenaline produced a decrease in forearm blood flow while adrenaline had the reverse effect. Since the response with noradrenaline occurred at a time when the blood pressure was raised, it was felt that the change was due to contraction of muscle vessels by the drug.

The authors studied the circulatory changes in 3 cases of pheochromocytoma and concluded that the alterations associated with the paroxysmal attacks might be caused by the release of adrenaline and noradrenaline from the tumor. The chronic hypertension in 2 cases was not due to the secretion of the tumor and was not relieved by operation. The authors were of the opinion that in essential hyper-

tension, noradrenaline is not present in abnormal amounts in the circulating blood.

ABRAMSON

Landen, H. C.: The Electrocardiographic Signs of Oxygen Deficiency in the Clinical Picture of Pulmonary Tuberculosis. Deutsche med. Wchnschr. **75**: 635 (May), 1950.

Abnormalities of the electrocardiogram consisting of S-T depression and T wave inversion, usually in leads II and III, can be seen in various types of pulmonary disease. In certain conditions like tuberculosis, bronchial asthma, bronchiectasis, pneumonia, and carcinoma, the abnormal electrocardiogram can be acutely improved by breathing of pure oxygen for about 15 minutes. The author concludes changes in the electrocardiogram in pulmonary disease do not necessarily indicate myocardial disease. They may be due to unsaturation of the arterial blood with oxygen in disturbances of the respiratory function of the lungs. Such changes are reversible, but may become irreversible in a longer course of pulmonary disease. The effect of oxygen inhalation on the abnormal electrocardiogram can be used as a clinical test.

PICK

Brownlee, W. M., Waters, E. M., and McClendon, S. J.: Paroxysmal Supraventricular Tachycardia in Infancy. Am. J. Dis. Child. **79**: 838 (May), 1950.

The authors report the case of a 10 week old infant hospitalized because of a heart rate of 300 per minute. The electrocardiogram revealed a supraventricular tachycardia. Digitalis was administered every six hours. The child became pale, listless, and anorexic, and the temperature became elevated. Penicillin therapy was started and the digitalis dose increased. Cyanosis and groaning respirations became evident the following day and all medication was discontinued. Then, two minutes after the administration of 1 mg. of Methacholine chloride subcutaneously, the heart rate dropped to 140 per minute. Three hours later the pulse rate was 350 per minute and the color mottled. Methacholine chloride, 1 mg., was again administered and the heart rate fell to 70 per minute. Recovery was uneventful. The authors state this to be the first reported case in which Methacholine was successfully used to abolish paroxysmal tachycardia in infancy.

MARGOLIES

Kneese de Mello, H.: Contribution to the Study of the Direction of the T Wave in Unipolar Limb Leads. Arq. brasil. cardiol. **3**: 243 (June), 1950.

In order to determine, by a simple analysis of the electrocardiogram, whether or not the T waves in the unipolar limb leads are abnormal, the author studied this deflection in 1000 consecutive tracings including bundle branch block, ventricular hypertrophy, and normal cases. A negative T wave in leads aV_L and aV_F was found in 257 tracings, which were divided into three groups: (1) inverted T waves in lead aV_L; (2) inverted T waves in lead aV_F; and (3) inverted T waves in both leads. All patients were carefully examined both clinically and roentgenologically.

The author concludes that a negative T wave in aV_L, following a positive QRS complex, is strongly suggestive of myocardial damage. Most cases correspond to left ventricular hypertrophy or myocardial ischemia. It is possible, however, to find a T wave inversion in aV_L as the only abnormality of the electrocardiogram. In the presence of isoelectric or negative QRS complexes, an inverted T wave as the sole finding is not necessarily abnormal. On the basis of an inverted T wave in lead aV_F, it is not justifiable to establish the diagnosis of myocardial damage. The inversion of this deflection both in lead aV_L and aV_F is always associated with other abnormalities and only occurs in pathologic cases.

SCHLESINGER

Limon Lason, R., Rubio Alvarez, V. and Bouchard, F.: Intracardiac Catheterization. Arch. Inst. cardiol. Mexico **20**: 271 (June), 1950.

The authors report the data of 17 cases studied by catheterization of the left heart. No complications occurred either during or after the procedure. The method was used in order to obtain simultaneous records of intraventricular pressure and electrocardiogram from the left ventricle.

Postmortem examination of a patient who died several weeks after catheterization failed to reveal any lesion attributable to the procedure, in the endocardium of the left ventricle, the aortic values or the coronary arteries.

LUISADA

Halonen, P. I., and Koskimies, A.: Electrocardiographic Changes in Connection with the Anthelmintic Use of Filicin. Cardiologia **17**: 1 (July), 1950.

The authors report electrocardiographic observations following anthelmintic treatment with the extract of Filicinmaris (3 to 5 Gm.). Out of 22 patients, 8 showed depression of S-T and inversion of the T wave in at least one of four leads. These changes were observed 2 to 4 hours after administration of the drug in all 8 cases, persisted 6 to 12 hours in 6 cases, and 24 hours in 1 case. With one exception, all of the patients were older than 50 years, which would suggest that anthelmintic treatment with Filicin should be used with caution in elderly subjects.

PICK

Koelbing, H.: Changes of the Electrocardiogram in Normal Persons under the Influence of Cardiac Glycosides. Cardiologia **17**: 79, 1950.

The author studied the effect of digitoxin (1.25 to 1

mg. given orally) and Strophosid (0.5 to 1 mg. given intravenously) on the electrocardiogram of 6 normal young subjects. Changes consisted of a slight and transient slowing of the heart rate (7 to 9 beats for not more than 24 hours) and flattening of the T wave. The average reduction in the height of the T wave, calculated by determination of the T vector in the frontal plane, was 30 to 40 per cent. This alteration persisted for three days following intravenous strophanthin and up to seven days after oral digitalis; no correlation was found, however, between the dose of the glycoside and the extent of the electrocardiographic changes. Dihydroergotamine and Bellafolin did not affect changes of the T wave produced by the two glycosides, which would indicate that digitalis has a direct effect on the myocardium, independent of the vegetative nervous system.

PICK

Holzmann, M.: Amyloidosis of the Heart. With Special Reference to the Electrocardiogram. Ztschr. f. Kreislaufforsch. **39:** 401 (July), 1950.

The author describes electrocardiographic observations in a 58 year old woman with atypical amyloidosis which at autopsy was restricted mainly to the heart. The changes of the electrocardiogram consisted in sinus tachycardia, second degree atrioventricular block with Wenckebach periods, low voltage of all waves, including the P waves, in all leads, and a pattern in the precordial leads resembling that seen in anterior wall infarction (QS and inverted T wave). Histologic examination of the heart revealed nodular and diffuse distribution of amyloid in the walls of both auricles and ventricles and in the intraventricular septum, accounting for the multiplicity of the anomalies in the electrocardiogram.

PICK

Chardon, G. and Gross, A.: Electrocardiographic Modifications and Orthostatism. Compt. rend. Soc. de Biol. **144:** 1042 (Aug.), 1950.

The authors studied the circulatory effects produced by passive positional changes in dogs under deep chloralose anesthesia. Sudden elevation of the animal to a vertical position was followed by a sudden increase in heart rate amounting to almost 100 per cent. The rate rose proportionally with the degree of elevation. The arterial pressure showed negligible variations and no changes of origin or conduction of the cardiac impulse could be detected in the electrocardiogram. Tachycardia produced by section of the four depressor nerves was not affected by changes in position of the animal.

The authors conclude that cardiac acceleration in the vertical position is reflex in origin, is mediated by "barosensible" nerves and serves the purpose of preventing orthostatic hypotension.

PICK

Kistin, A. D., and Brill, W. D.: Clinically Significant Differences between Precordial Electrocardiograms Derived From V and CF Leads. Ann. Int. Med. **33:** 636 (Sept.), 1950.

The authors reported seven cases in which there were clinically significant differences between precordial electrocardiograms derived from V and CF leads recorded in succession, the precordial electrode remaining in the same place. Abnormalities occurred in the CF leads, which consisted of inverted T waves, and in two cases abnormal Q waves, whereas the corresponding V leads were normal. There was no definite evidence of heart disease in any of the cases, although there were questionable symptoms or signs in some. The general conclusion is that the CF leads gave false indications of cardiac disease, while the normal V leads were more consistent with the cardiac status. In two of the cases the diagnosis of myocardial infarction might have been made from the CF leads when there was nothing in the history to suggest the occurrence of infarct or angina pectoris. The discrepancies were due to high potentials at the left leg compared to the potentials at the precordium and at the Wilson electrode; such potentials may occur in the absence of heart disease and may be related to alterations in the position of the heart and its relationship to adjacent structures.

WENDKOS

Thaon, M.: Contribution to the Study of the Electrocardiogram of Premature Newborns. Arch. d. mal. du coeur **43:** 826 (Sept.), 1950.

Electrocardiograms obtained from 18 cases of premature new born infants (weight 1200 to 2800 Gm.) showed the following pattern: large P waves, a P-R interval of 0.06 sec., and a QRS of 0.04 sec. duration and of small amplitude, with marked S waves in I and II. The QRS vector, determined from the limb leads, had a position between +90 and +150 degrees and measured 1 to 2 Ashman units. S-T was often convex and notched and the T wave small and usually inverted in III. V_R and V_L showed mainly inverted complexes, while the epicardial pattern of the left ventricle (qR) was found in V_F. The precordial leads revealed inversion of the RS ratio (tall R in V_1 and deep S in V_7) and inversion of T from V_1 to V_5.

The electrocardiogram of the newborn premature infant differs in certain features from that found in an infant born at term. The differences are attributed by the author to a relative hypertrophy of the auricles and of the right ventricle, to a more marked vertical position and clockwise rotation, and to some disturbance of repolarization present in the heart of the premature infant.

PICK

Bellet, S., Gazes, P. C., and Steiger, W. A.: The Effect of Potassium on the Electrocardiogram in

the Normal Dog and in Dogs with Myocardial Infarction. Am. J. M. Sc. **220**: 237 (Sept.), 1950.

The electrocardiographic effects of potassium administration were studied in 31 dogs: 9 normal, 12 with acute infarction, 6 with healed infarcts, one endocardial potential study in the normal and one in an animal with acute infarction, and in 2 the reversibility of the effects after toxic doses.

Three patterns of T and S-T changes were observed: (a) the normal pattern, consisting of increase in amplitude of T with narrowing of the base and depression of the S-T segment; (b) the intermediate type, observed in hearts with small infarcts involving chiefly the endocardial portion of the left ventricle, consisting of diminution in amplitude of the already inverted T wave; and (c) the acute infarction pattern, observed in transmural infarcts, and characterized by an increase in amplitude of the inverted T wave, its configuration practically an inverted image of that seen in the normal. Subsequent toxic effects consisted of bundle branch block, ventricular tachycardia, and bradycardia, and were observed both in normal and in infarcted animals.

The terminal cardiac mechanism was cardiac arrest in the normals and ventricular fibrillation in most instances of the infarcted group. There was no evidence of cumulative potassium effects. Even at the stage of marked QRS changes and ventricular tachycardia, the effects were reversible upon cessation of the potassium administration.

The data suggest a limited value in the use of potassium to differentiate between the inverted T wave of myocardial infarction and other conditions; its use is probably not without added risk. In man hyperpotassemia is usually complicated by the presence of alterations of other electrolytes. This adds to the complexity of the clinical picture and the electrocardiographic pattern.

DURANT

Wenger, R., Hofman-Credner, D. and Hortnagel, W.: The Conduction of the Impulse in the Auricles. Direct and Semidirect Electrocardiographic Leads in the Human Heart. Ztschr. f. Kreislaufforsch. **39**: 653 (Nov.), 1950.

The authors studied electrocardiograms from various points in the cavity of the right auricle and obtained esophageal leads from different levels in both normal and diseased hearts. The beginning of the "intrinsicoid" deflection was used for the determination of the arrival of the impulse at points nearest the tip of the electrode, the location of which was determined fluoroscopically.

In cases with P mitrale, a local delay of impulse conduction could be demonstrated in the left auricle, while the activation of the right auricle was completed in normal fashion. Cases with P pulmonale did not reveal any abnormality of impulse propagation. A focal block within the right auricle was suggested in some cases in which the auricular intrinsicoid deflection was delayed in the middle part of the right auricular cavity, compared with auricular waves obtained from the region of the inferior vena cava.

Auricular potentials obtained from the pulmonary artery correspond usually to right auricular potentials, but may be subject to variations due to rotation of the heart and varying anatomic relationship of the vessel.

PICK

Meneses Hoyos, J.: A Study of the Electrocardiogram in Pre-agonal States. Arch. d. mal. du coeur **43**: 934 (Oct.), 1950.

The author presents the electrocardiograms of a man of 43 recorded during uremic coma which terminated in death. The tracings obtained were similar to those obtained by the author in experimental animals. The author had studied the mechanism of the slowly dying heart in rabbits, dogs and guinea pigs over a period of 13 years. He describes a pattern which seems to be independent of the immediate cause of death. The sequence of events is usually the following: the sinoauricular rhythm is replaced by auricular fibrillation; then, the ventricular systoles become more and more infrequent until they disappear completely. A certain interval elapses between clinical death and cessation of any electrical activity. This interval was found to last 15 to 45 minutes in animals, not more than 8 minutes in man. In all the cases studied by the author, a bundle branch block was present sooner or later. The ventricular complexes become broad and monophasic in the terminal period assuming the type which the author calls "agonal ventricular complex." The best time for revival of the heart is before the appearance of this pattern and the best results are obtained by the use of mechanical procedures.

LUISADA

Biork, G., Sylvan, T., and Lindblom-Tillman, G.: Electrocardiographic Studies during Angiocardiography. Acta cardiol. **5**: 509, 1950.

Forty-eight patients were studied electrocardiographically before, during and following angiocardiography. Transient disturbances of the heart rate and rhythm were almost regular findings when the dye was injected through a catheter into a cardiac chamber or into the pulmonary artery. Premature beats of supraventricular or ventricular origin, the latter sometimes of "left ventricular contour," were observed in 20 out of 22 cases during injection into the right auricle or right ventricle and especially during direct injection of the pulmonary artery. They occurred either as single premature beats or in the form of shorter or longer runs. One case developed auricular fibrillation during the catheterization and another ventricular tachycardia. Coronary disturbances (S-T depression and T inversion) were occasionally noted during aortographies when the

tip of the catheter entered, or was placed close to, the opening of a coronary artery. Electrocardiograms taken a few days after the injection or later showed no persistence of the disturbances.

The observed anomalies can usually be correlated with the time of the injection and are probably elicited by the spout of the injected material or by the impact of the catheter at the moment of the injection. Since they represent a potential risk to the patient, the authors recommend continuous electrocardiographic control by a direct writing machine during angiocardiography.

PICK

Sanabria, T.: Contribution to Anatomic-Clinical Studies of Bundle Branch Block. Acta Cardiol. **5**: 527, 1950.

In 6 cases with the electrocardiographic pattern of bundle branch block microscopic study of the entire conduction system, including serial sections through the atrioventricular node and both bundle branches, revealed no anatomic lesion which could account for the conduction defect. Two cases are described in detail. The first with a typical "left bundle branch block" showed nodular infiltration, resembling Aschoff bodies, throughout the myocardium of the left ventricle. The other, a case of syphilitic heart disease with a right bundle branch block pattern in the electrocardiogram, had a marked stenosis of the ostium of the right coronary artery and multiple microspic foci of old and recent necrosis scattered throughout the free wall of the right ventricle. The author describes an additional case of complete atrioventricular block with QRS complexes of normal duration and configuration despite complete interruption of both bundle branches by fibrous tissue.

In view of these morphologic findings the author feels that the generally accepted concept of bundle branch block needs revision.

PICK

Segers, M., Regnier, M., Van Heerswynghels, J., and Hendricks, J.: The Vectorcardiogram of Various types of Intraventricular Block. Acta Cardiol. **5**: 521, 1950.

The author used vectorcardiography in an attempt to verify the concept of a peripheral origin of various "bundle branch block" patterns. Widening and notching of the QRS complex, if present in all leads of the electrocardiogram, goes along with a grossly irregular and widened QRS loop in the vectorcardiogram. This is attributed by the authors to a conduction disturbance distributed diffusely throughout the free wall of the ventricles. This type, which includes the so-called common type of bundle branch block is termed by the authors "major block". A deformation of the initial part of the loop indicates subendocardial localization and an irregularity of the terminal part subepicardial localization of the conduction defect ("minor blocks"). The latter is represented by electrocardiograms which show notching of the terminal parts of the QRS like the various "S-types of bundle branch block." The configuration of the vector loop in the presence of a intraventricular conduction defect depends—in the opinion of the authors—entirely on the type of block (major or minor) and not on its localization in the right or left side of the heart.

PICK

Boydjian, N. and Van Dooren, Fr.: A Study of Two Cases of Bilateral "Bundle Branch Block". Contribution to the Localization of Intraventricular block. Acta Cardiol. **5**: 532, 1950.

Electrocardiograms of two cases are presented, which in the opinion of the authors are typical instances of bilateral intraventricular conduction defects. The characteristic features were widened R and S waves in lead I and a delayed intrinsicoid deflection in right as well as in left precordial leads. Electrokymograms showed delayed ejection of the left ventricle in one case and no difference of right or left ventricular ejection time in the other case. The typical delay of the intrinsicoid deflection may not show up in the customary precordial leads but can be demonstrated in additional leads taken from higher or lower intercostal spaces. In such cases the conduction defect cannot be located in the main bundle branches; circumscribed areas of block leading to delay of impulse conduction within the free walls of the ventricles appear the more likely cause of the electrocardiographic changes.

PICK

Peter, G.: The Electrocardiogram during Hypoxia and its Alterations by Sympathicolytic Agents. Cardiologia **17**: 98, 1950.

The changes in the electrocardiogram produced by inhalation of a mixture containing 8 to 9 per cent of oxygen were studied in 20 persons with a neurovegetative syndrome and in 29 patients with chronic coronary disease. S-T depression of more than 2 mm. in a single lead was graded as an abnormal (positive) effect. Marked reduction of the T wave was classified as slightly positive, if the sum of associated S-T depression in all leads was more than 3 mm., and as probably positive, if this sum was less than 3 mm.

Using these criteria the author found an abnormal electrocardiographic response in more than half of the patients with coronary disease, and three times in patients with neurovegetative disturbances. The effect of sympatholytic drugs upon the abnormal electrocardiogram was inconsistent in both groups. In some of the cases it remained abnormal, whereas in others it reverted to the control pattern. The author concludes that the use of sympatholytic drugs is of no definite value in the differentiation of electrocardiographic changes due to coronary disease

from those due to functional disturbances of the vegetative nervous system.

PICK

Villani, G., and Tenci, R.: A Study of Extertional Bundle Branch Block. Folia cardiol. **9**: 175, 1950.

The authors report a case of intermittent bundle branch block occurring only after effort; they review the etiology. The authors consider that the most likely cause was coronary arteriosclerosis. This would leave a good coronary flow during rest, while the flow would become relatively insufficient during exertion. This disturbance is frequently a prelude to permanent bundle branch block.

LUISADA

Buchman, D. M.: The Wolff-Parkinson-White Syndrome. Report of a Case Illustrating Also the Post-Tachycardia Syndrome. Wisc. Med. J. **49**: 1127 (Dec.), 1950.

The author reviews the essential features of the Wolff-Parkinson-White syndrome. A woman aged 24 years who demonstrated this syndrome is described. The patient had been a professional dancer, able to participate in strenuous physical effort. Serial electrocardiograms taken after an episode of tachycardia accompanied by syncope disclose variations in the configuration of the S-T segment and T waves which are attributed by the author to the post-tachycardia syndrome. The patient had chronic cholelithiasis which was treated surgically after the episodes of tachycardia appeared. This gave rise to speculation regarding the relation of the two conditions.

ROSENBAUM

Donzelot, E., Zade, A. M. E., de Balsac, R. H., and Metiau, C.: Study of the Electrocardiograms of 314 Patients with Congenital Heart Disease. Acta Med. Scandinav. **136**: 159, 1950.

In a series of 314 patients with congenital heart disease, 264 were cyanotic and 200 of these had the tetralogy of Fallot. Changes in ST and T portions of the electrocardiogram were frequent, occurring in about half of the cyanotic and noncyanotic groups. Right axis deviation was found in 274 cases, while 15 had left axis deviation. Prolongation of the QRS interval chiefly due to right bundle branch block was present in 6.6 per cent of cases. One third of the subjects had abnormalities of the P waves; prolonged P-Q intervals (over 0.20 sec.) were found in 6.6 per cent of instances. Arrythmias were present in 5 per cent; only 1 instance of complete heart block was found.

WAIFE

HYPERTENSION

Hilden, T.: Hypertensive Encephalopathy Associated with Hypochloremia. Acta med. Scandinav. **136**: 199 (Jan.), 1950.

The author describes 5 cases characterized by acute cerebral disturbances, hypertension, and transient fall in plasma chlorides and increases in blood urea. In none of the cases did the laboratory findings or the course of the illness resemble those of chronic glomerulonephritis, although 2 were diagnosed as chronic pyelonephritis. It is important that plasma chlorides and blood urea values should be investigated in all cases of acute encephalopathy. The relationship between electrolyte disturbances and cerebral symptoms have assumed greater importance because of the wide use of the salt poor diet in hypertension. With sodium chloride restriction the result may be marked hypochloremia and an increase of the blood urea, and cerebral symptoms or even death may follow. In the present series 3 cases were treated with parenteral saline with improvement in their condition, and this treatment is therefor suggested for hypertensive encephalopathy with hypochloremia.

SCHWARTZ

Blacket, R. B., Depoorter, A., Pickering, G. W., Sellers, A. L., and Wilson, G. M.: Hypertension Produced in the Rabbit by Long Continued Infusions of Renin. Clin. Sc. **9**: 223 (May), 1950.

The effect of the continuous intravenous infusion of renin on the level of blood pressure was studied in a series of rabbits. It was found that a relatively constant hypertension followed such a procedure and persisted during the entire experimental period. With progressively increasing doses of renin, however, smaller rises in blood pressure occurred, until with the highest dosage tested, the degree of hypertension tended to fall.

According to the authors, their findings of a sustained rise of blood pressure, at least for two weeks, supported the view that hypertension following renal artery constriction is due to the release of renin into renal vein.

ABRAMSON

Assali, N. S.: Studies on Veratrum Viride: Standardization of Intravenous Technique and its Clinical Application in the Treatment of Toxemia of Pregnancy. Am. J. Obst. & Gynec. **60**: 387 (Aug.), 1950.

The author attempts to evaluate the action of veratrum viride in the treatment of toxemia of pregnancy and to establish a standard dosage and a technic for intravenous administration of this drug. Ten patients with pre-eclampsia were used as subjects for the standardization, and 15 patients with convulsive eclampsia for the study of the therapeutic effects of intravenous injection of the material.

Because of the complex nature and variability of the composition of crude preparations of veratrum, no standard effective dose has been established. The present study, however, suggests that the depressor action of the drug is not reached until

0.2 cc. is given intravenously. Smaller doses are ineffective, whereas larger quantities, although invoking a marked depressor action, produce intolerable side reactions. The hypotensive effect of 0.2 cc. lasts for approximately an hour, and its magnitude is not altered by repeated injections of the drug.

Clinically, the intravenous administration of veratrum viride in severe cases of eclampsia seems to be of great value. Convulsive seizures are rapidly controlled, and the patient becomes conscious and rational in a short period of time. The drug may be given in 5 per cent glucose and water, with the rate regulated so as to deliver an hourly amount of 0.2 cc. of the material. Or it may be administered in the form of single injections of the same amount every hour. Blood pressure and pulse rate are recorded every five minutes. After the general condition of the patient has improved, veratrum should be given subcutaneously until the time of delivery.

ABRAMSON

Eisenberg, S., Buie, R., Jr., and Tobian, L., Jr.: Adrenal Cortical Function in Essential Hypertension. A Study of Sweat Sodium Concentration. Am. J. M. Sc. **220:** 287 (Sept.), 1950.

It is very unlikely that ordinary essential hypertensives have any considerable increase in the level of "electrolyte-influencing" adrenal cortical steroids, since the sweat sodium concentration is not significantly different from that of normotensive subjects.

DURANT

Judson, W. E., Culbertson, J. W., Tinsley, C. M., Litter, J., and Wilkins, R. W.: The Comparative Effect of Small Intravenous Doses of Epinephrine Upon Arterial Pressure and Pulse Rate in Normotensive Subjects and in Hypertensive Patients before and after Thoracolumbar Sympathectomy. J. Clin. Investigation **29:** 1405 (Oct.), 1950.

The authors found that when small intravenous doses of epinephrine are administered there is characteristically a short hypertensive phase occurring 15 to 25 seconds after injection; a transient hypotensive phase is manifest at 25 to 35 seconds; and a more sustained hypertensive phase is observed at 55 to 70 seconds.

There were no qualitative differences in the blood pressure response in normotensive as compared with hypertensive patients before or soon after thoracolumbar sympathectomy. No evidence was found to indicate that hypertensive patients are more sensitive than normotensive subjects to the pressor effect of single intravenous doses of epinephrine, or that such patients become more sensitive after sympathectomy.

WAIFE

Westerborn, A.: Results of Operation (Splanchnicotomy) for Hypertension. A Follow-Up Study of 47 Cases. Acta Med. Scandinav. Suppl. **246:** 268, 1950.

The author reports the results of splanchnicotomy in 47 patients with hypertension. Thirty-eight were classified as having essential hypertension and nine were considered to have malignant hypertension. The ages of the patients ranged from 27 to 61 years. Eight patients died of diseases of the heart, vessels or kidneys at intervals ranging from one month to four and one-half years after the operation. Twenty-three patients were considered healthy or markedly improved with no disability at intervals of one to six years postoperatively; some of these individuals had persistent hypertension.

In this series the blood pressure seldom fell to normal and in general after an abrupt postoperative decline, it rose to 30 to 40 mm. below pre-operative level and sometimes to the original value. A normal blood pressure developed in only 13 per cent of the cases. Of the 9 cases of malignant hypertension, 6 died during the follow-up period, one committed suicide and in the remaining 2 the follow-up period had been too short for adequate evaluation.

ROSENBAUM

PATHOLOGIC PHYSIOLOGY

Wilkins, R. W., Bradley, S. E., and Friedland, C. K.: The Acute Circulatory Effects of the Head-Down Position (Negative G) in Normal Man, with a Note on Some Measures Designed to Relieve Cranial Congestion in This Position. J. Clin. Investigation **29:** 940 (July), 1950.

A study was performed on 42 subjects, tilted into the head-down position, in order to establish the basic pattern of circulatory changes in man under such conditions. Subjectively, the patients experienced severe pain in the shoulders because of the weight of the body upon them, a sense of warmth, flushing and congestion of the face and cranial swelling. The nasal mucosa became congested, producing partial or total obstruction. The feet grew cold and clammy.

Blood pressure, measured by means of a needle in the femoral artery, fell quickly and then more slowly to reach a constant level. The first drop was considered to be passive as a result of the hydrostatic effect, while the second indicated vasodilatation. In the brachial artery there was usually a rise or no change.

Cerebral venous pressure increased in the head-down position as the result of hydrostatic forces, minimized to some extent by certain moderating mechanisms. The authors felt that the cranial congestion, as indicated by the high venous pressure, was the chief cause for the symptoms associated with the head-down position.

ABRAMSON

Sloan, H. E.: The Vagus Nerve in Cardiac Arrest; the Effect of Hypercapnia, Hypoxia and Asphyxia on Reflex Inhibition of the Heart. Surg., Gynec. & Obst. **91:** 257 (Sept.), 1950.

Because of the gravity of cardiac arrest in the

course of a surgical operation, the author attempted to investigate the factor of stimulation of the vagus in its inception. The study was performed on 36 dogs, anesthetized with morphine and urethane and under artificial respiration. Electrical stimulation of the intact vagus nerve at the hilum of the lung did not produce cardiac arrest, regardless of the intensity of the stimulus. Only when the animals were subjected to marked, progressive hypoxia or asphyxia did this procedure produce inhibition of the heart, which was followed frequently by temporary cardiac standstill when the oxygen deficiency was extreme.

The author concluded that, if these experiments on the dogs had any application to similar reactions in the human being during operation, it would appear that under conditions of adequate oxygenation, reflex inhibition of the heart by stimulation of the vagus nerve will not result in cardiac arrest. Vagal reflexes arising during intrathoracic operations may, however, play a part in augmenting an existing oxygen deficiency and may aid in producing cardiac arrest under conditions of severe hypoxia or asphyxia.

ABRAMSON

Assali, N. S., and Prystowsky, H.: Studies on Autonomic Blockade. II. Observations on the Nature of Blood Pressure Fall with High Selective Spinal Anesthesia in Pregnant Women. J. Clin. Investigation **29:** 1367 (Oct.), 1950.

The blood pressure response to high selective spinal anesthesia was studied on 17 normal pregnant subjects, and 4 patients with pre-existing essential hypertension associated with pregnancy. The fall in pressure was found to be unrelated to loss of skeletal muscle tone or to anoxia. At the time of maximum fall in blood pressure, there was a significant decrease in cardiac output. It appears that spinal hypotension was related to venous stagnation in the lower extremities, for it could be prevented by use of blood pressure cuffs inflated to suprasystolic pressure or by 90 degree elevation.

The authors discuss two hypotheses to explain this finding. The blood pressure of normal women at term may be maintained by increased neurogenic tone possibly in both arterioles and veins. When this tone is blocked by high selective spinal anesthesia both vascular systems collapse, the arteriolar to a greater degree. This results in increased vascular capacity of the legs, followed by decreased venous returned to the heart, decreased cardiac output, and drop of blood pressure. The phenomenon does not occur in toxemia of pregnancy, possibly because arteriolar and venous tones are maintained by different mechanisms. On the other hand, spinal hypotension could be caused by blockade of the compensatory homeostatic vasoconstrictor reflexes in different areas of the body. The pooling of blood in the legs serves to precipitate the blood pressure fall. Under such circumstances, the "exclusion" of the legs from the general circulation restores that small amount of blood to the systemic circulation which reestablishes circulatory adjustments.

WAIFE

PATHOLOGY

Neidhart, K., and Rumrich, R.: Myocarditis in Tuberculosis. Deutsche med. Wchnschr. **75:** 667 (May), 1950.

The authors observed 6 patients between 15 and 24 years of age with acute onset of fever, cutaneous "rheumatic" manifestations (erythema nodosum) and transient changes in the electrocardiogram (inversion of T in the standard leads) considered to be characteristic of myocarditis. Within 8 to 12 weeks, signs of acute tuberculosis developed in all cases, and one case died of miliary dissemination.

Tuberculous allergic myocarditis occurs especially in primary tuberculous infection of the adult, but is less common than tuberculous pleuritis.

PICK

Fisher, E. R.: Polyarteritis Nodosa Involving the Female Genital Tract. Am. J. Obst. & Gynec. **60:** 445 (Aug.), 1950.

The author reports the case of a comatose patient who died shortly after being admitted to the hospital. At autopsy, the acute necrotizing arteritis of polyarteritis nodosa was found in the uterus, cervix and ovaries, as well as in the kidneys, spleen and intestinal tract. The gynecologist must look upon polyarteritis nodosa as a disease which may confront him, especially in the differential diagnosis of gynecologic complaints associated with bizarre systemic symptoms.

ABRAMSON

Jones, R. S., and Frazier, D. B.: Primary Cardiovascular Amyloidosis: Its Clinical Manifestations, Pathology and Histogenesis. Arch. Path. **50:** 366 (Sept.), 1950.

The authors state that primary amyloidosis of the cardiovascular system is fairly common, its true incidence not being realized because of the failure of both clinical and pathologic recognition. They collected 15 cases in 600 consecutive autopsies of subjects over 20 years of age; almost all these cases were above the age of 50. Approximately one half of them were the "mild form" of the disease, a type not clinically diagnosable. The "severe form" leads to myocardial failure and death.

When 50 per cent or more of the cardiac weight is due to amyloid deposit, the heart is enlarged and its action generally arrhythmic. The sounds are weak, and the electrocardiogram shows low voltage and an unusual incidence of auricular fibrillation. Hypertension is often fluctuating and without evidence of visceral arteriosclerosis. The disease is slowly progressive and congestive heart failure may continue

for long periods (up to six years), in the experience of the authors. The usual signs of systemic amyloidosis are not present in this special cardiac type of the disease. Hyperglobulinemia and a positive congo red test are usually absent. Hypertrophic arthritis and parasthesia (numbness) complicate many cases, and an increased risk for surgery and anesthesia has been noted.

Pathologically, the myocardium is unusually firm, grayish red and waxy on cross section. The walls of the heart, emptied of blood, do not collapse, and in this respect the thin-walled right auricle is notable. The auricular endocardium is studded with minute sandlike particles, pale gray or light brown. The right auricle is more involved than any other chamber. The triscuspid valve and the coronary arteries are occasionally sites of deposit. Histologically, the reticulum is thickened and eventually is replaced by amyloid "rings" which encroach on the myocardial fiber. The latter gradually disappears as a result of pressure atrophy.

GOULEY

Friedman, N. H., and Silverman, J. J.: Benign Pericardial Effusion in the Course of Chronic Myelogenous Leukemia. Case Report. Blood **5:** 916 (Oct.), 1950.

The authors point out that, although it is not uncommon to find an excessive amount of fluid in the pericardium in the late stages of leukemia, pericarditis with effusion is rarely seen as an incidental complication of this disease. The presence of fluid in the pericardium may be due to myocardial failure, contributed to by the pronounced anemia, fever, and elevated basal metabolism. Defects in coagulation and changes in capillary fragility may result in the fluid's being bloody. In an occasional case, there may be actual invasion of the myocardium or pericardium by leukemic cells. Pericardial effusion, however, may be incidental and benign, unrelated to the leukemia.

A case of chronic myelogenous leukemia in a 28 year old white woman is reported, in which, seven months after the discovery of the disease and the induction of a remission with Fowler's solution, the patient complained of precordial pain. A pericardial effusion was diagnosed and serosanguinous fluid, which failed to clot, was found by pericardial tap. Because of clinical and hematologic evidence of a relapse of the leukemia, x-ray therapy was directed to the spleen. While under observation, the pericardial friction rub disappeared, and the electrocardiogram and roentgenogram of the chest reverted to normal. The patient lived two years after this with no evidence of a recurrence of the pericardial effusion, but required further treatment for the leukemia. No autopsy was obtained.

BEIZER

Gore, I.: The Question of Traumatic Heart Disease. Ann. Int. Med. **33:** 865 (Oct.), 1950.

Traumatic heart disease includes cases of cardiac failure or coronary thrombosis precipitated by strenuous effort; cardiac lesions or injuries resulting in prompt death, such as a penetrating wound or a myocardial rupture from sudden forceful compression occurring in high speed accidents; myocardial trauma, with delayed rupture and ruptured heart valves and a variable survival period lasting in some cases for many years; the initiation or augmentation of cardiac symptoms or of disturbed cardiac activity by a traumatic incident. In order to establish a valid diagnosis of traumatic heart disease, it is necessary to record objective evidence of cardiac injury and to obtain corroborative data from the history. As soon as possible after the traumatic episode, therefore, it is important to ascertain (a) the condition of the patient prior to the trauma or physical effort; (b) his antecedent activities for at least a week; (c) his customary habits; (d) the behavior pattern prior to the accident, especially any neurotic traits; (e) the exact degree of injury or strain; and (f) the departure of the patient from his normal equilibrium after the episode.

If death ensues, the autopsy findings are extremely important, provided they are properly interpreted. To illustrate the importance of properly interpreted findings in suspected cases of traumatic heart disease, the author includes a detailed case report concerning a 23 year old male who suffered a direct injury to the chest and, seven days later, developed left ventricular failure and died. During the seven-day survival period, there was a profound degree of shock, accompanied by abnormal physical and electrocardiographic findings which could be considered to be consistent with a severe cardiac injury. The autopsy findings were indicative of a myocarditis of longer than seven days duration, however, and not diagnostic of a traumatic lesion. Therefore, the nonpenetrating chest injury was considered to be responsible for death only insofar as it acted as a trigger mechanism, which precipitated abnormal cardiac activity in a case with pre-existing heart disease.

WENDKOS

PHARMACOLOGY

Wylie, E. J., Gardner, R. E., Johansen, R., and McCorkle, H. J.: An Experimental Study of Regional Heparinization. Surgery **28:** 29 (July), 1950.

Experiments were performed on 5 dogs to test a method for the continuous intra-arterial injection of heparin. The femoral artery and vein were exposed under aseptic conditions and a purse string suture placed in the superficial layers of the arterial surface of the vessel. In the center of the suture an incision was made, and one end of a Polythene tube was introduced into the artery and the suture tightened. A No. 20 hypodermic needle was inserted in the

opposite end and connected to a flask containing heparin in normal saline solution. The dilute heparin solution was allowed to drip into the artery at a uniform rate, utilizing a pressure reservoir to overcome the arterial pressure. The infusion was adjusted to a rate sufficient to maintain a coagulation time of 15 minutes in the blood obtained from the corresponding vein. Under such circumstances general heparinization did not occur, as indicated by the lack of noticeable effect on the coagulation time of blood taken from the antecubital vein.

On the basis of experimental data from the use of heparin to protect arteriotomy wounds from thrombosis, it was concluded that regional heparinization should be maintained for at least 72 hours.

ABRAMSON

Fremont, R. E., and King, H.: Digitoxin Causing Ventricular Tachycardia with Peripheral Vascular Collapse. J. A. M. A. **143:** 1052 (July), 1950.

A case of ventricular tachycardia with peripheral vascular collapse following a single oral dose of 0.6 mg. digitoxin is reported in a 57 year old white man. The paroxysm was abolished by intravenous administration of quinine dihydrochloride, and the collapse was overcome with the help of plasma infusion. The danger of giving an average full digitalizing dose of 1.2 mg. of digitoxin is emphasized. The suggestion is made that the potent digitoxin glycoside should be used judiciously, particularly in elderly patients with arteriosclerotic heart disease and in those with renal failure; the use of digoxin is preferred for them. Plasma or blood infusion is recommended for the treatment of shock precipitated by paroxysmal tachycardias.

KITCHELL

Redisch, W., and Brandman, O.: The Use of Vasodilator Drugs in Chronic Trench Foot. Angiology **1:** 312 (Aug.), 1950.

The effects of vasodilator drugs on the symptoms of chronic trench foot were studied in 100 ambulatory patients. Aminophylline, papaverine, Etamon, and oral Priscoline were found to be of no value. Both intravenous Priscoline and Roniacol tartrate by mouth appeared to alleviate symptoms. The most important measure of improvement was the patient's ability to work longer hours, to stand or to walk longer, or to work outdoors or in a cold room. The side effects of Roniacol tartrate were inconsequential, and the drug was given safely over prolonged periods.

WESSLER

Stubbs, J. B., and Woolsey, R. D.: Angina Pectoris. Treatment by Injection of Stellate Ganglia with Ammonium Sulfate. South. M. J. **43:** 675 (Aug.), 1950.

Eighteen patients with angina pectoris had bilateral stellate ganglia block performed with 20 cc. of a buffered ammonium sulfate solution (Dolamine). Complete relief of anginal pain was obtained in 72 per cent, with partial relief in 28 per cent of cases. There were no failures. Reinjection was performed on the average of every three or four months. The authors feel this is a simple, quick, and effective method with advantages over alcohol injections or surgical procedures.

WAIFE

Basset, A., Ducoux, F., and Mertmeau, H.: Presence of a Cardiodepressive Substance in Extracts of Burned Muscle of the Frog. Compt. rend. Soc. de biol. **144:** 1048 (Aug.), 1950.

The authors found that addition of an extract of cauterized skeletal muscle to the immersion fluid of an isolated and beating frog heart produces the following effects: a progressive slowing of the rate of contractions terminated by standstill in diastole; in the electrogram, there is progressive deformation and disappearance of QRS and/or T waves; and a loss of excitability occur consisting of failure of the immersed heart to respond by contraction to mechanical stimuli. All these phenomena are reversible if the immersion fluid is renewed, and the experiment may be repeated several times until the depression of the main cardiac functions becomes definite and irreversible. These observations may contribute to the understanding of circulatory accidents occurring in man following major burns.

PICK

Jourdan, F., and Chattonet, J.: Demonstration of a Peripheral Vasoconstrictive Action of Tetraethyl Ammonium Bromide. Compt. rend. Soc. de biol. **144:** 1063 (Aug.), 1950.

The authors report that if the spinal column in a dog is destroyed and the connection of peripheral vessels with the vasomotor centers thus completely interrupted, intravenous injection of tetraethylammonium bromide, in doses of 10 to 15 mg. per Kg., is followed by a distinct hypertensive reaction. An adrenaline effect can be excluded since the heart rate remains unchanged during the experiment. The pressure elevation is ascribed by the authors to a direct peripheral action of the drug upon vascular musculature. A similar reaction can be obtained in the normal organism by repeated application of high doses of tetraethylammonium, the hypertensive reaction manifesting its effect following blockage of the ganglionic synapse by the preliminary dose.

PICK

Bellet, S., Steiger, W. A., and Gazes, P. C.: The Effect of Different Grades of Myocardial Infarction upon the Tolerance to Potassium: An Experimental Study in Dogs. Am. J. M. Sc. **220:** 247 (Sept.), 1950.

Isotonic potassium chloride (1.14 per cent) was administered intravenously at a rate of 10 cc. per minute to normal dogs and to dogs with acute and

chronic myocardial infarctions. Normal dogs died at serum concentrations of 13.9 to 18 mEq. per liter of potassium. Dogs with minor degrees of myocardial damage showed a similar lethal concentration. Dogs with moderate to severe grades of infarction, both acute and chronic, showed a significant decrease in the lethal serum concentration at death. Intraventricular block (regarded as a definite evidence of potassium toxicity) developed at a significantly lower level in all types of acutely infarcted dogs as compared to the normal. In 6 dogs with healed myocardial infarction, there was no significant change in the serum concentration at which intraventricular block occurred, but death occurred at a slightly lower concentration as compared to the normal control. With the method of potassium administration used, the rise in serum potassium did not appear to be a linear function of time. The sequence usually seen was an initial rapid rise, then a tendency to plateau, followed by a terminal increase in slope.

DURANT

Sutton, G. C., Kappert, A., Real, A., Skoglund, K. H., and Nylin, G.: The Effect of L-Nor-Epinephrine upon the Corpuscular Volume and Hematocrit. Am. Heart J. **40:** 369 (Sept.), 1950.

The authors have studied the effect of intravenous l-norepinephrine (0.07 mg.) on the corpuscular volume and hematocrit of 10 young subjects with normal cardiovascular systems. The corpuscular volume was determined by the use of erythrocytes tagged with radioactive phosphorus. For the group, the mean heart rate was decreased by 18 beats per minute while the systolic and diastolic pressures were elevated 23 and 17 mm. Hg, respectively. The large (antecubital) vein hematocrit increased 2.3 per cent within two minutes after the injection. There was no alteration in the circulating corpuscular volume. This study indicates that norepinephrine, like epinephrine, produces a rise in hematocrit without a detectable increase in corpuscular volume. A redistribution of a portion of the cellular constituents from the contracted peripheral smaller vessels to the larger vessels has been held responsible for the elevated hematocrit. In addition, there is a withdrawal of a portion of plasma from the actively circulating blood stream, shifting it to the smaller vessels of the periphery and in part to the interstitial compartment. The latter action may contraindicate the use of norepinephrine in the therapy of some types of shock where effective withdrawal of some plasma is not desirable.

HELLERSTEIN

Bayliss, R. I. S., Etheridge, M. J., Hyman, A. L., Kelly, H. G., McMichael, J., and Reid, E. A. S.: The Effect of Digoxin on the Right Ventricular Pressure in Hypertensive and Ischaemic Heart Failure. Brit. Heart J. **12:** 317 (Oct.), 1950.

Because of conflicting views of the action of Digoxin, the authors recorded optically the right ventricular pressure for about one hour following the intravenous injection of 1 to 1.5 mg. in 15 patients with hypertensive and ischemic heart failure.

Eight of the 15 developed a rapid rise in arterial pressure of more than 10 mm. Hg systolic or diastolic which passed off within half an hour. In 3, the rise was particularly marked; in 2 of these 3, the cardiac output fell, whereas in the third it remained unchanged. All 3 became increasingly dyspneic and orthopneic, and 1 developed pulmonary edema. Ten showed a fall in systolic and end diastolic pressures, with only 4 of these showing a rise in cardiac output. Two showed a significant rise in cardiac output, without significant alteration in right ventricular pressures.

The authors conclude that Digoxin commonly improves the emptying of the left ventricle and diminishes the volume of residual blood, thereby lowering the diastolic filling pressure. With a lowering of the pulmonary vascular pressure, the diastolic intraventricular pressure falls. Digitalis likewise has a pressor effect on the systemic arterioles, however, and may affect various functional states of the myocardium differently. Hence, the resultant effect of digitalis may differ from patient to patient.

SOLOFF

Clagett, A. H., Jr.: Intravenous Use of Quinidine, with Particular Reference to Ventricular Tachycardia. Am. J. M. Sc. **220:** 381 (Oct.), 1950.

The efficacy of quinidine in the treatment of paroxysmal ventricular tachycardia has been established by others. The purpose of this study was to determine the relative safety of quinidine lactate when given intravenously. In 13 patients treated, the dose varied from 0.4 Gm. to 3.25 Gm., and the smallest dose given which was followed by return to regular sinus rhythm was 0.8 Gm. Except for nausea and vomiting in 3 patients, there were no symptoms even slightly suggestive of toxicity. The author prefers the intravenous route of administration over the intramuscular, because when properly administered (well diluted and given slowly under constant observation) intravenous quinidine lactate can be discontinued immediately upon the restoration of normal rhythm or at the first sign of toxicity. Given in this manner, it is relatively safe and may well be lifesaving, particularly in patients developing ventricular tachycardia following myocardial infarction, in whom regular sinus rhythm cannot be re-established by oral quinidine, or whose condition is so critical as to demand the greatest possible speed of action.

DURANT

Levy, J.: Oxygen Therapy of Bundle Branch Block. Am. J. M. Sc. **220:** 400 (Oct.), 1950.

The author discusses the causes of bundle branch

block in the light of anatomic, physiologic and pathologic changes which may alter conduction in the bundle of His and its terminal branches. The return to normal conduction in patients with bundle branch block may be spontaneous, or may occur upon rest or following diuretic therapy. Three patients were studied who had left bundle branch block associated with arteriosclerotic heart disease. In each of these cases the inhalation of oxygen eliminated the conduction disturbance. The author emphasizes the fact that the early use of oxygen may prevent irreversible changes in the conducting tissue induced by anoxia. The restoration of one patient to an active life from one of invalidism occurred following the cessation of bundle branch block.

SHUMAN

Glass, W. H.: Rutin Therapy in Diffuse Capillary Bleeding; Ineffectiveness When Fragility Tests are Normal, Am. J. M. Sc. **220:** 409 (Oct.), 1950.

Numerous studies on the clinical effectiveness of rutin in the management of bleeding states has led to considerable doubt in regard to its therapeutic value for these conditions. In this report, 5 patients with hereditary hemorrhagic telangiectasia received rutin for two to three years without significant alteration of their bleeding tendencies. There was no evidence of diffusely increased capillary fragility as manifested by the Rumpel-Leede or Göthlin indexes. The striking tendency toward spontaneous variations in the extent of the lesions and bleeding in these patients in re-emphasized. One additional case of increased capillary fragility of undetermined etiology with a history of bruising on minimal trauma was studied. This patient had strongly positive capillary fragility tests which were decreased to normal, as were her clinical bleeding phenomena, following rutin therapy using 50 mg. three times daily. Vitamin C given prior to rutin had not altered the clinical state.

SHUMAN

Stanbury, J. B., and Farah, A.: Effects of the Magnesium Ion on the Heart and on Its Response to Digoxin. J. Pharmacol. & Exper. Therap. **100:** 445 (Dec.), 1950.

The authors studied the effect of the magnesium ion on dog hearts (denervated and heart-lung preparations). The rate of the sinoatrial node was slowed proportionally to the serum magnesium concentration by a direct action independent of nervous influences. With artificially induced atrial flutter the atrial rate was slowed and eventually normal rhythm was restored by the magnesium ion. Increasing the serum concentration of magnesium resulted in a lowering of the systemic output and a diminution of the competence of the heart. Because of the decrease in rate, however, stroke volume and coronary flow were increased. Addition of calcium ion restored the competence of the heart without affecting the coronary flow. Studies on the antagonism of the magnesium ion and digoxin indicated that increasing the magnesium level prior to administration of digoxin had little effect in increasing the toxic or lethal dose of digoxin. However, in cases with ventricular irregularities caused by digoxin, the rapid addition of magnesium chloride could temporarily restore normal rhythm in the heart-lung preparations, in intact dogs, and in dogs with denervated hearts.

SAGALL

Winder, C. V., Thomas, R. W., and Kamm, O.: Relative Experimental Coronary Vasodilator Potencies of Papaverine and Its Ethyl Analogue, Ethaverine (Diquinol, Perparin). J. Pharmacol. & Exper. Therap. **100:** 482 (Dec.), 1950.

The authors studied the comparative effects of papaverine and its ethyl analog (ethaverine) on the coronary outflow of surviving isolated rabbit hearts. The two drugs were about equal in peak potency as coronary vasodilators when injected quickly. At the lowest dose levels the two drugs approached equality in the total coronary vasodilating action. At intermediate and higher dose levels 1.5 to 2.0 times as much papaverine as ethaverine was required for equal total increase in coronary flow. Ethaverine appears, therefore, to have a greater effective potency than papaverine.

SAGALL

Brigden, W., and Sharpey-Schafer, E. P.: Postural Changes in Peripheral Blood Flow in Cases with Left Heart Failure. Clin. Sc. **9:** 3, 1950.

The authors studied the effects of "feet-down" and "feet-up" positions on blood flow in the forearm in 12 patients with some degree of left heart failure and in 6 other subjects with hypertensive or aortic disease who did not complain of postural dyspnea. In all patients with left heart failure the forearm flow decreased in the "feet-up" position and increased in the "feet-down" position. These responses were the opposite to those observed in normal subjects or in cardiac patients not in congestive heart failure. No alteration in blood flow with postural changes was noted when the nerves to the forearm were blocked by procaine.

The results were interpreted as indicating that a rise in central venous pressure results in constriction of forearm vessels. In normal subjects great changes in pressure are needed to effect such a readjustment while in patients with congestive heart failure even small alterations are effective in this regard. The mechanism appears to be a reflex of which the efferent pathways are the vasomotor nerves.

ABRAMSON

PHYSICAL SIGNS

Lian, C., and Welti, J. J.: Systolic Rhythms with a "Three Sounds Tempo." Acta cardiol. **5:** 109, 1950.

The systolic rhythms with a "three sounds tempo" can be divided into two types according to the appearance of the extra sound. The protosystolic type, in which the extra sound is superimposed upon the second half of the first sound, sometimes lengthening it, is a phenomenon more often of pulmonary than of aortic origin; and the protosystolic pericardial vibration, a phenomenon of the apical area. The meso- or telesystolic type is due to the adding to the normal heart sounds of a snap, perceived in the apexoxyphoid area and provoked by a momentary tension of apleuropericardial adhesion. This snap is sometimes followed by a telesystolic murmur.

The arterial splitting of the first sound, the protosystolic pericardial vibration, and the pleuropericardial meso- or telesystolic snap are entirely distinct in their clinical characteristics and meaning: they should be called by different names. It is inappropriate to call them "systolic gallop rhythms." After a short historical review, the authors emphasize the fact that the name "gallop rhythm" should be restricted to the pathologic diastolic sounds caused by an irregular filling of an insufficient ventricle. To make "gallop rhythm" a synonym of "three sounds tempo" can only lead to confusion.

AUTHORS

PHYSIOLOGY

Jourdan, F., and Duchene-Marullaz, P.: On Cardio-Accelerator Tone. Compt. rend. Soc. de biol. **144:** 859 (June), 1950.

The authors studied the influence of cardio-accelerator tone in order to explain the rapid and variable heart rate found normally in the rabbit. Bilateral extirpation of the stellate ganglia was performed on three rabbits and the heart rate followed by numerous electrocardiograms before and following the operations. Unilateral stellectomy was ineffective; however, when followed by the same operation on the other side, a permanent and marked fall of pulse rate (up to 30 per cent) and disappearance of its spontaneous variations was observed.

The authors conclude that both the sympathetic and parasympathetic system may exert a tonic action upon the heart of mammals. While in the dog the parasympathetic tone is dominant and the accelerator tone weak, the conditions are reversed in the rabbit. Thus the dominance of one system is apparently accompanied by a complete or almost complete extinction of the tonic function of its antagonist.

PICK

Cerletti, A., and Weissel, W.: Contribution to the Problem of the So-Called Time of Isometric Contraction (Anspannungszeit) of the Heart. Helvet. Physiol. et Pharmacol. Acta **8:** C 14 (July), 1950.

The authors studied the time relationship between the beginning of the ventricular complex in the electrocardiogram, and the beginning of the pressure curve of the left ventricle in anesthetized dogs (obtained by cardiac catheterization) and the relationship between the former and the beginning of the mechanical contraction (determined by a plethysmographic method). The time interval between the onset of electrical and mechanical events was found to be 10 to 15 sec. per 1000, while the interval between the beginning of the electrocardiogram and that of the pressure curve measured 30 to 50 sec. per 1000. The authors conclude that interval usually called "time of isometric" contraction ("Anspannungszeit") is actually composed of two separate events of the cardiac cycle namely, a shorter "electromechanic latency" and a longer "electropressoric latency."

AUTHORS

Henry, J. P., and Gauer, O. H.: The Influence of Temperature upon Venous Pressure in the Foot. J. Clin. Investigation **29:** 855 (July), 1950.

The effect of the local application of heat on the venous pressure of the foot was measured in 12 normal subjects. The readings were obtained by inserting a needle into a dorsal vein of the foot with the subject standing erect. With the onset of vasodilatation in response to local application of heat, there was a definite increase in mean venous pressure which could not be reduced below 70 mm. Hg even by vigorous walking movements. This level was definitely higher than the combined forces which prevent movement of fluid out of the blood vessel into the tissue spaces, namely, the intersititial tissue pressure in the skin of the foot and the osmotic pressure of the plasma proteins.

The authors conclude that the results help explain the swelling of dependent regions, such as the ankles, so often noted in hot weather. The obese individual, who must dissipate heat by vasodilatation rather than by conduction through the superficial body layers, and the patient who cannot sweat normally may be expected to show an increased incidence of heat edema.

ABRAMSON

Tcheng, K. T.: Histologic Study of Cardiac Innervation of the Dog. Compt. rend. Soc. de biol. **144:** 882 (July), 1950.

The author studied efferent sympathetic and parasympathetic fibers in the walls of all chambers of the dog heart, and found that the sympathetic innervation was prevalent and abundant, especially in the left ventricle. Afferent fibers were less numerous and are present mainly in the left auricle. No nervous elements were found along the course of the common bundle of His and both its branches. However, the node of Tawara has a very rich innervation by both excitatory and inhibitory fibers and thus seems to be an important, if not the only, center over which reflexes are conveyed from the auricle to the

ventricles. Nerve fibers are also present in the proximity of the Purkinje elements. The coronary vessels of the dog have a rich vagal and sympathetic innervation, penetrating into the tunica mediums. Sensory fibers can be demonstrated in all three layers of the coronary arteries.

PICK

Gray, S. J., and Sterling, K.: Determination of Circulating Red Cell Volume by Radioactive Chromium. Science **112:** 179 (Aug.), 1950.

When radioactive chromium (half-life 26.5 days) is added to blood in vitro, it is taken up avidly by the red cells. The radioactivity persists for one day or more after injection into experimental animals. Since the exchange of Cr^{51}: between red cells and plasma is negligible for 24 hours, this isotope appears ideal for tagging red cells. The reliability of the method in a series of experiments on dogs is reported.

WAIFE

Montgomery, H., and Horwitz, O.: Oxygen Tension of Tissues by the Polarographic Method. I. Introduction: Oxygen Tension and Blood Flow of the Skin of Human Extremities. J. Clin. Investigation **29:** 1120 (Sept.), 1950.

The authors present a method for making estimations of oxygen tension in intact human skin. A platinum electrode was used to measure electrical current. The electrode is calibrated by insertion into excised dead skin immersed in solutions of varying oxygen tensions. The method apparently measures oxygen tension of skin tissue and not that of blood.

It was found that the oxygen tension of the skin greatly diminished during cutaneous vasoconstriction. In normal subjects oxygen inhalation of varying concentrations changed the oxygen tension of the vasodilated skin of the extremities in proportion to the concentration in the inhaled mixture. Oxygen inhalation only moderately increased the low oxygen tension in the skin of extremities made ischemic by occlusive arterial disease.

WAIFE

Schloerb, P. R., Friis-Hansen, B. J., Edelman, I. S., Solomon, A. K., and Moore, F. D.: The Measurement of Total Body Water in the Human Subject by Deuterium Oxide Dilution. J. Clin. Investigation **29:** 1296 (Oct.), 1950.

Using the stable hydrogen isotope deuterium as "heavy water" (deuterium oxide), total body water was determined in 17 normal young male subjects. The values ranged from 55.9 per cent to 70.2 per cent with an average of 61.8 per cent of body weight. The average of 11 normal females was 9.9 per cent less. This substance, when given intravenously, apparently reaches equilibrium with body water within two hours; the equilibrium time of deuterium oxide after oral or subcutaneous administration is about three hours. Deuterium was excreted in the urine at a rate of 0.1 per cent of the administered amount per hour. Of the indexes studied, total body water was correlated most closely with surface area and oxygen consumption.

WAIFE

Walker, A. J., and Longland, C. J.: Venous Pressure Measurement in the Foot in Exercise as an Aid to Investigation of Venous Disease in the Leg. Clin. Sc. **9:** 101, 1950.

The authors studied changes in venous pressure in the legs of 27 patients under varying conditions, using direct cannulation of a vein on the dorsum of the foot with flexible polythene tubing.

With the normal patient in the standing position, readings of approximately 90 mm. Hg. were obtained, while during exercise the level fell to around 40 mm. Hg, as a result of the compressing action of the muscles on the patient, yielding veins with functioning valves. Similar findings were observed in patients with lymphatic edema. In patients with varicosities, exercise pressures remained much higher than in normal subjects. However, the use of a tourniquet, to obstruct the superficial veins below the knee, reduced the exercise pressure to about normal levels.

In the group of patients either with a thrombosed or an incompetent femoral vein, the exercise pressure was high and remained high even when a tourniquet was applied below the knee. These two groups were differentiated by the phlebogram which showed a patent femoral vein in the patients with incompetent femoral valves. Ligation of the popliteal vein in such subjects produced a marked reduction of the exercise venous pressure in approximately half the cases. In these subjective improvement was also noted. On the other hand, ligation of the superficial femoral vein could not be shown to improve the venous function.

ABRAMSON

Thurnher, B., and Weissel, W.: Visualization of the Movements of the Pulmonary Artery. A Contribution to the Problem of Indirect Measurements of the Pressure in the Lesser Circulation. Cardiologia **16:** 78, 1950.

The author studied kymograms obtained from the inferior lobe branch of the right pulmonary artery during normal respiration and during forced expiration against graded and known pressures. In normal respiration, the kymogram of normal persons showed signs of expansile pulsation, while in cases of pulmonary congestion and sclerosis of the pulmonary artery, only transmitted movements were present. During forced expiration against a pressure of 20 to 30 mm. Hg, the expansile pulsations of normal subjects were replaced by transmitted pulsations, which ceased completely with expiration against maximal pressure. However, the high intra-

tracheal pressures necessary to obtain the latter phenomenon could be achieved only in a few normal subjects. The method is, therefore, not yet suitable for estimation of the degree of pulmonary hypertension.

PICK

v. Tschermak-Seysenegg, A.: A Physiologic Comparison of the Embryonic and the Developed Heart. Cardiologia **16:** 370, 1950.

The author presents a comparative study of certain physiologic properties of the embryonic and fully developed fish heart. The embryo heart shows very early rhythmic automatism and conductivity, before the development of muscle fibrils and at a time when it is not yet under the influence of the nervous system. It follows, like the adult heart, the "all or none" law and has a refractory period. The latter extends throughout most of the diastole so that the embryonic heart responds only rarely to premature external stimuli. However, if there is a response to premature stimulation, a compensatory pause follows the extrasystole. Conduction can be shown to be bidirectional in all stages of development.

These observations confirm the primary myogenic origin of the basic properties of the heart and their independence from the development of the nervous system. The latter exerts a quantitative effect on certain functions of the heart, like the duration of the refractory period.

PICK

RHEUMATIC FEVER

Stollerman, G. H., and Bernheimer, A. W.: Inhibition of Streptolysin S by the Serum of Patients with Rheumatic Fever and Acute Streptococcal Pharyngitis. J. Clin. Investigation **29:** 1147 (Sept.), 1950.

The authors performed studies on a group of 75 cases of rheumatic fever, and 33 cases of untreated acute streptococcal pharyngitis which revealed that eighty per cent of patients with rheumatic fever showed a tendency for the serum level of streptolysin S inhibitor to fall below normal values during rheumatic activity and to return to normal levels during convalescence.

A low streptolysin S inhibitor titer was encountered in some cases of unrelated disease, and the fall did not appear to be specific for rheumatic fever. There was no significant change in this titer among the cases of streptococcal pharyngitis. The streptococci isolated from the throats of patients with both pharyngitis and rheumatic fever were capable of producing streptolysin S in vitro. It appears therefore that the capacity of the serum to inhibit streptolysin S is due to a normal component of serum rather than to a specific antibody.

WAIFE

Wroblewskin, F., and Messinger, W. J.: Active Rheumatic Carditis in Patients over 40 Years of age. Am. Heart J. **40:** 345 (Sept.), 1950.

The authors studied 34 patients over 40 years of age who had histologically active rheumatic heart disease. The criteria consisted of acute and chronic inflammatory involvement of the valves and/or myocardium, according to the standards of the New York Heart Association. Of the 32 cases in which complete clinical data were available for the study, 10 patients exhibited classic or obvious signs of clinical activity; 16 patients gave adequate evidence of clinical activity; and 6 patients showed minimal or no manifestations of clinical activity. A correct antemortem diagnosis could have been made, if suspected, in the first two groups. Smoldering clinical rheumatic activity is not rare in patients over 40 years of age; unexplained fever and unusual (toxic) responses to digitalis may be clues to the diagnosis.

HELLERSTEIN

ROENTGENOLOGY

Meneses Hoyos, J., and Gomez del Campo, C.: Angiography of the Thoracic Aorta by Direct Puncture Methcd. Arch. d. mal. du coeur **43:** 996 (Nov.), 1950.

The authors describe a new method of visualization of the thoracic aorta by direct puncture of the aortic arch and rapid injection of 50 cc. of a 70 per cent solution of Nosylan. During the injection, an x-ray is taken. The ascending aorta, the aortic arch and the descending aorta were clearly outlined by this procedure. In two cases, the coronary arteries and the semilunar valves were also made visible.

Eight patients were studied by this technic of applied direct aortography. No accidents occurred. The method proved useful for the diagnosis of doubtful or obscure cases.

LUISADA

SURGERY IN HEART AND VASCULAR SYSTEM

Bauer, G.: Division of Popliteal Vein for Varicose Ulceration. Brit. M. J. 4674: 318 (Aug.), 1950.

The author found that ulcers of the lower leg, are almost always accompanied by other complaints, such as chronic pitting edema, large areas of brawny and indurated skin, and the complaint of dull aching pain in the limb when placed in the vertical position. These criteria constitute the components of the "lower-leg-stasis syndrome." The etiologic agent in many cases is a previous deep venous thrombosis in which recanalization has occurred, with the result that the vein is now a thick-walled rigid tube without even traces of valves. The absence of these structures is responsible for the venous stasis.

On the basis of such a view, the author divided the popliteal vein in 245 patients with ulcers of the legs to prevent the possibility of back-flow. It was subsequently found, through radiographic methods,

that the contractions of the calf muscles drove the blood through numerous fine-calibered channels into the muscle veins of the thighs. This was encouraged by the use of some type of supporting bandage for at least two months after the operation. Marked improvement was observed in all the patients. The aching or bursting pain was relieved almost at once, and the ulcers generally healed in a shorter time than would have been expected with conservative treatment. There were no postoperative deaths and no complications, aside from slight wound hematomas in 5 cases.

A follow-up study was performed in 196 cases, and in 165 of these the ulcers had remained completely healed. The indurative changes showed considerable regression and in many cases had disappeared entirely. In the remaining 31 patients recurrence of symptoms was observed.

ABRAMSON

OTHER SUBJECTS

DeWind, L. T., and Jones, R. J.: Cardiovascular Observations in Dystrophia Myotonica. J. A. M A. **144:** 299 (Sept.), 1950.

The authors reviewed 98 cases of dystrophia myotonica in which electrocardiograms and the heart and circulatory system were studied. Electrocardiograms of persons under 45 years of age were compared with those made on persons over 45. It was found that in a total of 67 patients under 45 years of age there were 57 per cent with abnormal electrocardiograms and in 16 patients over 45 there were 62 per cent with abnormal electrocardiograms. The abnormalities of most frequent occurrence were low P waves, prolonged P-R intervals, prolonged intraventricular conduction time and elevation of the S-T segment. The findings do not appear to be related to any significant cardiac, physical or roentgen findings, and cannot be attributed to coronary disease or to the quinine frequently administered to these cases. It is felt that the myocardium may itself be involved in dystrophia myotonica by the same process that affects the skeletal muscle.

KITCHELL

Mallory, G. K., Blackburn, N., Sparling, H. J., and Nickerson, D. A.: Maternal Pulmonary Embolism by Amniotic Fluid: Report of Three Cases and Discussion of the Literature. New England J. Med. **243:** 583 (Oct.), 1950.

The authors present an analysis of 20 cases (3 new and 17 previously published) of amniotic fluid embolism. The patient is usually a multigravida and the fetus is usually large. The catastrophe is ushered in by violent uterine contractions and premature rupture of the membranes, after which cyanosis, dyspnea, and shock occur. Death usually supervenes within an hour. The diagnosis is made pathologically by the presence of formed elements of the amniotic fluid in the pulmonary arterioles and capillaries. However, the degree of mechanical pulmonary obstruction seems insufficient alone to explain death. Additional factors which may be involved are reflex vasospasm, circulatory embarrassment due to overloading of the circulation by large amounts of amniotic fluid, and anaphylaxis.

HANNO

Porter, W. B., Clark, O., and Porter, R. R.: Nonspecific Benign Pericarditis. J. A. M. A. **144:** 749 (Oct.), 1950.

In the records of 219 patients with acute pericarditis, the authors found 14 patients whose symptoms and clinical course justified the diagnosis of nonspecific benign pericarditis. The diagnosix of angina pectoris or coronary occlusion had been tentatively made in 8 of the cases and was mentioned as a possibility in all of them. The occurrence of a friction rub, fever, accelerated sedimentation rate and abnormality of electrocardiogram in all cases resulted in superficial similarity between the two conditions. All of these patients survived the acute episode and none have shown residual disease in a follow-up period varying from 14 years to nine months. Pain and symptoms of a cold, sore throat, or influenza-like infections preceded the onset in all the patients. Pericardial friction accompanied the pain from the beginning of the illness and fever was a consistent clinical manifestation. Accelerated sedimentation rates occurred in all patients. Teleroentgenograms on 8 patients showed obvious increase in heart size and pericardial aspiration was done in 4 cases with the removal of bloody fluid. The immediate and remote prognosis of nonspecific benign pericarditis was consistently good in these patients.

KITCHELL

Weiner, A. E., and Reid, D. E.: The Pathogenesis of Amniotic-Fluid Embolism: III. Coagulant Activity of Amniotic Fluid. New England J. Med. **243:** 597 (Oct.), 1950.

Because hemorrhagic phenomena are commonly found in cases of amniotic fluid embolism, and because amniotic fluid has been shown to possess a thromboplastin-like coagulant activity, the authors advance the theory that the entrance of amniotic fluid into the maternal circulation may evoke intravascular clotting with resultant thrombosis and secondary fibrinopenia with hemorrhagic manifestations.

HANNO

Berliner, R. W.: Renal Excretion of Water, Sodium, Chloride, Potassium, Calcium, and Magnesium. Am. J. Med. **9:** 541 (Oct.), 1950.

In this article the author discusses critically and constructively the numerous unsolved and intricate problems involved in studying the renal excretion of water, sodium, chloride, potassium, calcium, and magnesium. Knowledge of the mechanisms of electrolyte excretion and regulation is fragmentary at best. Available technics of study are deficient. The

puncture studies of individual nephrons have been very useful, but their scope is limited by immense technical difficulties. Perhaps the most important problem lies in the uncontrolled, unmeasured, and probably often unrecognized variables. It is premature to assign responsibility for various clinical abnormalities to one or another of the discrete renal functions or to any one of the extrarenal regulators of electrolyte excretion.

HARRIS

Rubin, I. L., and Flaum, G.: Acute Cor Pulmonale. Ann. Int. Med. **33**: 1013 (Oct.), 1950.

Phlebothrombosis in the veins of both legs resulted in repeated pulmonary infarctions in a previously healthy 22 year old white male. Throughout his illness, several repeated electrocardiograms remained essentially normal. Approximately 10 days after the initial evidences of embolism, there was noted in the second left intercostal space, near the parasternal line, a systolic pulsation, a rough systolic murmur and a systolic thrill. These physical signs persisted for about three weeks and then disappeared. They were ascribed to acute cor pulmonale with resultant temporary dilatation of the pulmonary artery. Follow-up examination, one year afterward, revealed no abnormalities of the lungs or cardiovascular system, except for slight edema of the legs on standing.

WENDKOS

Eisenmenger, W. J., Blondheim, S. H., Bongiovanni, A. M., and Kunkel, H. G.: Electrolyte Studies on Patients with Cirrhosis of the Liver. J. Clin. Investigation **29**: 1491 (Nov.), 1950.

The authors performed detailed metabolic studies on patients with advanced Laennec's cirrhosis. It was found that the restriction of ingested sodium to 14 to 20 mEq. per day effectively controlled ascites in the majority of this group. Because of minimal sodium excretion in the urine, dietary sodium should approximate fecal and dermal loss. After paracenteses, a precipitous fall in serum sodium was found. When extremely low levels of serum sodium was found it was believed to be secondary to maximal formation of ascites.

A rise in serum sodium and an increase in the urinary excretion of sodium seemed to indicate decreased ascites production before the associated changes in fluid balance were noted. During maximal production of ascites, sodium was retained by the body. There was also a decrease in sodium in the saliva and sweat, suggesting generalized retention, rather than only renal factors.

WAIFE

Brownell, K. A., Hartman, F. A., and Reiman, R. W.: Effect of Adrenal Enucleation on Serum Sodium. Endocrinology **47**: 326 (Nov.), 1950.

The authors demonstrated that enucleation of the adrenal glands, leaving the glomerular zone relatively intact, resulted in a decrease in serum sodium. The decrease in serum sodium following adrenal enucleation was most apparent in young rats two to four weeks after the enucleation. Many of the older rats showed no changes in serum sodium. Adrenal-enucleated and control animals showed a comparable drop in serum sodium following starvation.

CORTELL

Sims, E. A. H., Welt, L. G., Orloff, J., and Needham, J. W.: Asymptomatic Hyponatremia in Pulmonary Tuberculosis. J. Clin. Investigation **29**: 1545 (Nov.), 1950.

The authors report that 10 patients with tuberculosis, all showing advanced malnutrition, hypotension, and hypoalbuminemia, were found to have a persistent hyponatremia. Nine had far advanced pulmonary tuberculosis and one had miliary tuberculosis. These subjects showed no evidence of renal or adrenal insufficiency. There were no signs or symptoms suggestive of sodium depletion and no evidence of dehydration, peripheral circulatory failure, or hyperpotassemia. The concentration of sodium in the serum remained in the subnormal or low normal range despite their high daily intakes of salt. The renal tubular cells did respond to desoxicorticosterone acetate by increasing the reabsorption of sodium. The adrenal glands were normal in the 6 patients who were autopsied.

The authors suggest that the primary defect is a chronic reduction of cellular osmolarity. The result of this would be an abnormal excretion of sodium in an effort to reduce the tonicity of the extracellular fluids to conform with the primarily reduced tonicity of the intracellular fluid, but with the maintenance of normal body water volume.

WAIFE

Elkinton, J. R., Clark, J. K., Squires, R. D., Bluemle, L. W., Jr., and Crosley, A. P., Jr.: Treatment of Potassium Retention in Anuria with Cation Exchange Resins. Am. J. M. Sc. **220**: 547 (Nov.), 1950.

One of the problems encountered with the carboxylic ammonia exchange resins prior to the addition of potassium was the removal from the body of significant amounts of potassium together with sodium. The authors have used the non-potassium containing resin to remove potassium from the circulation of patients unable to excrete it because of renal insufficiency. The resin was most effective when administered orally; if poorly tolerated, however, it was given by enema as a 10 per cent suspension in water. By either route, it reduced the hyperkalemia associated with anuria and uremia. Two of the patients died within several days following the cessation of resin administration, one of respiratory complications. The third, a patient with post-transfusion anuria, had a slightly elevated serum potassium which returned to normal as urine formation reappeared, following the last resin enema.

Simultaneous removal of sodium in this patient increased the degree of acidosis, a condition which was corrected by the use of sodium bicarbonate. A brief outline of important aspects of the medical management of patients with acute anuria is included, together with the suggestion that the cation exchange resin should be useful in controlling serum potassium levels when the artificial kidney is unavailable.

SHUMAN

Benton, J. G., Brown, H., and Rusk, H. A.: Energy Expended by Patients on the Bedpan and Bedside Commode. J. A. M. A. **144:** 1443 (Dec.), 1950.

The authors studied 28 subjects, 15 of whom were cardiac patients and the remainder either normal or with some disease other than cardiac, to measure the energy expended using a bedpan as compared with a bedside commode. Tests were performed in all instances approximately two hours after a meal, after the subject had rested in bed for 15 minutes. Oxygen consumption in excess of resting was determined by means of a closed circuit respirometer, while the subjects were performing Valsalva maneuvers on the bedpan and on the bedside commode standardized conditions. There was no significant difference for each of the respective activities in the noncardiac and cardiac groups studied, but energy expenditure in terms of oxygen consumption above resting levels was consistently higher on the bedpan than on the commode. This test seems to demonstrate that besides the psychologic trauma of the use of a bedpan it is an unphysiologic procedure from the standpoint of energy cost. The supported sitting, or squatting, position is the optimum posture for defecation.

KITCHELL

Oppenheim, E., and Bruger, M.: Variations in Serum Cholesterol of Normal Rabbits after Injection of Hypercholesterolemic Rabbit Plasma. Proc. Soc. Exper. Biol. & Med. **75:** 636 (Dec.), 1950.

The authors performed this study to determine the effect of the intravenous administration of hypercholesterolemic rabbit plasma on the free and total serum cholesterol of normal rabbits.

The intravenous injection of hypercholesterolemic rabbit plasma in normal rabbits resulted in a rapid increase in the total serum cholesterol followed by a gradual decrease. The highest value was obtained in five minutes and in six hours or less the total serum cholesterol had reached the lowest postinjection level. In 24 hours, the total serum cholesterol was significantly increased above the six hour level with no significant alteration in the esterified cholesterol : free cholesterol ratio. Rabbits receiving normal rabbit plasma, normal saline or no injection showed little change in the total serum cholesterol at six hours. In 24 hours the total serum cholesterol likewise increased significantly compared to the six hour level. The rise in total cholesterol at 24 hours is apparently related to the mechanics of performing the experiment, i.e., the result of serial blood letting and/or trauma, rather than to the injection of cholesterol.

MINTZ

Forssman, O., and Stenqvist, H.: Paroxysmal Tachycardia Which the Patient Was Momentarily Able to Produce Himself. Acta Med. Scandinav. **136:** 323, 1950.

A 36 year old man was able to induce attacks of paroxysmal tachycardia by such actions as deep inspiration, the Valsalva experiment, and pushing the abdominal muscles forward while holding his breath. Carotid sinus pressure, ergotamine tartrate and prostigmine had no effect in producing these episodes. Moderate doses of quinidine for several weeks abolished the patient's ability to produce these attacks.

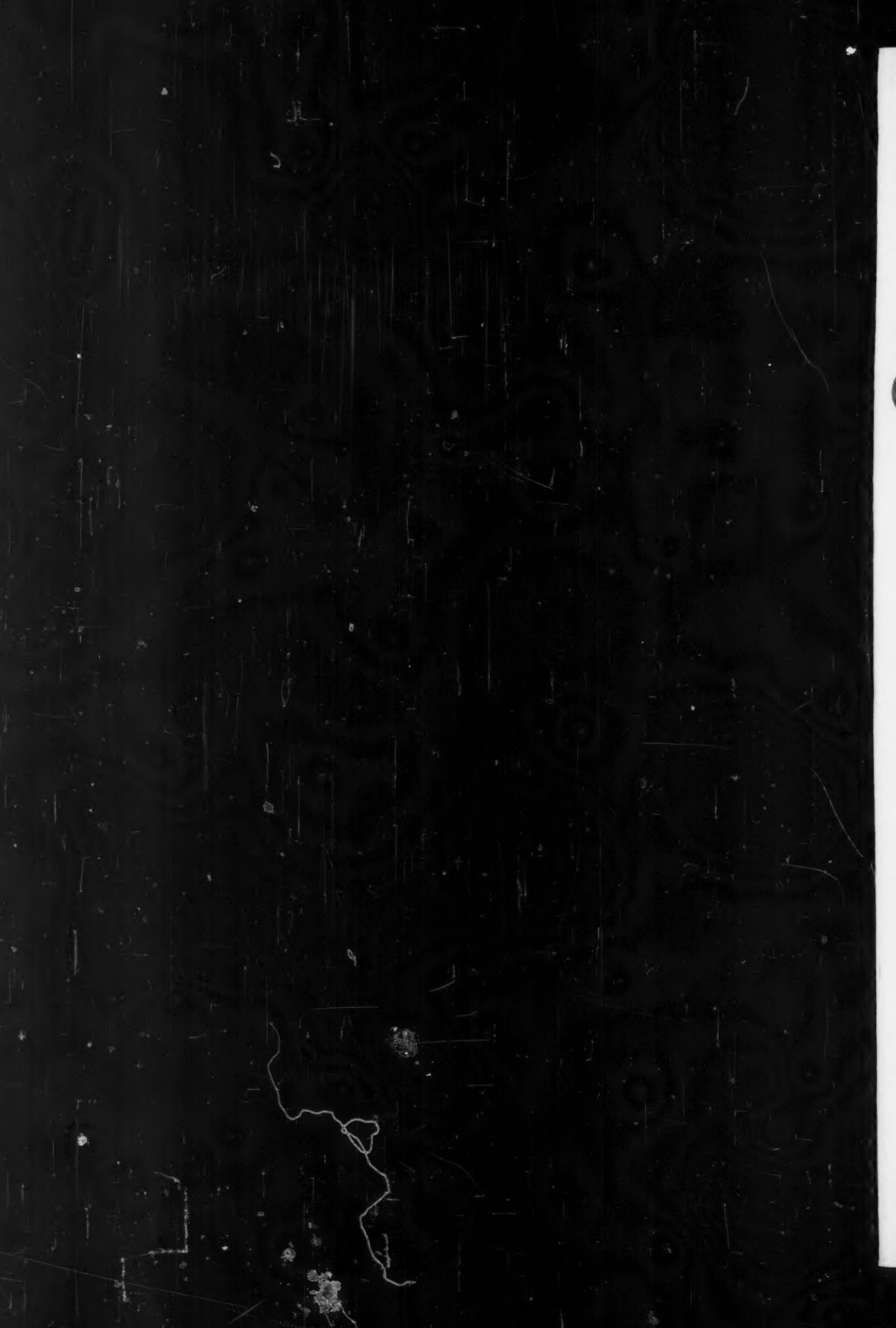
WAIFE

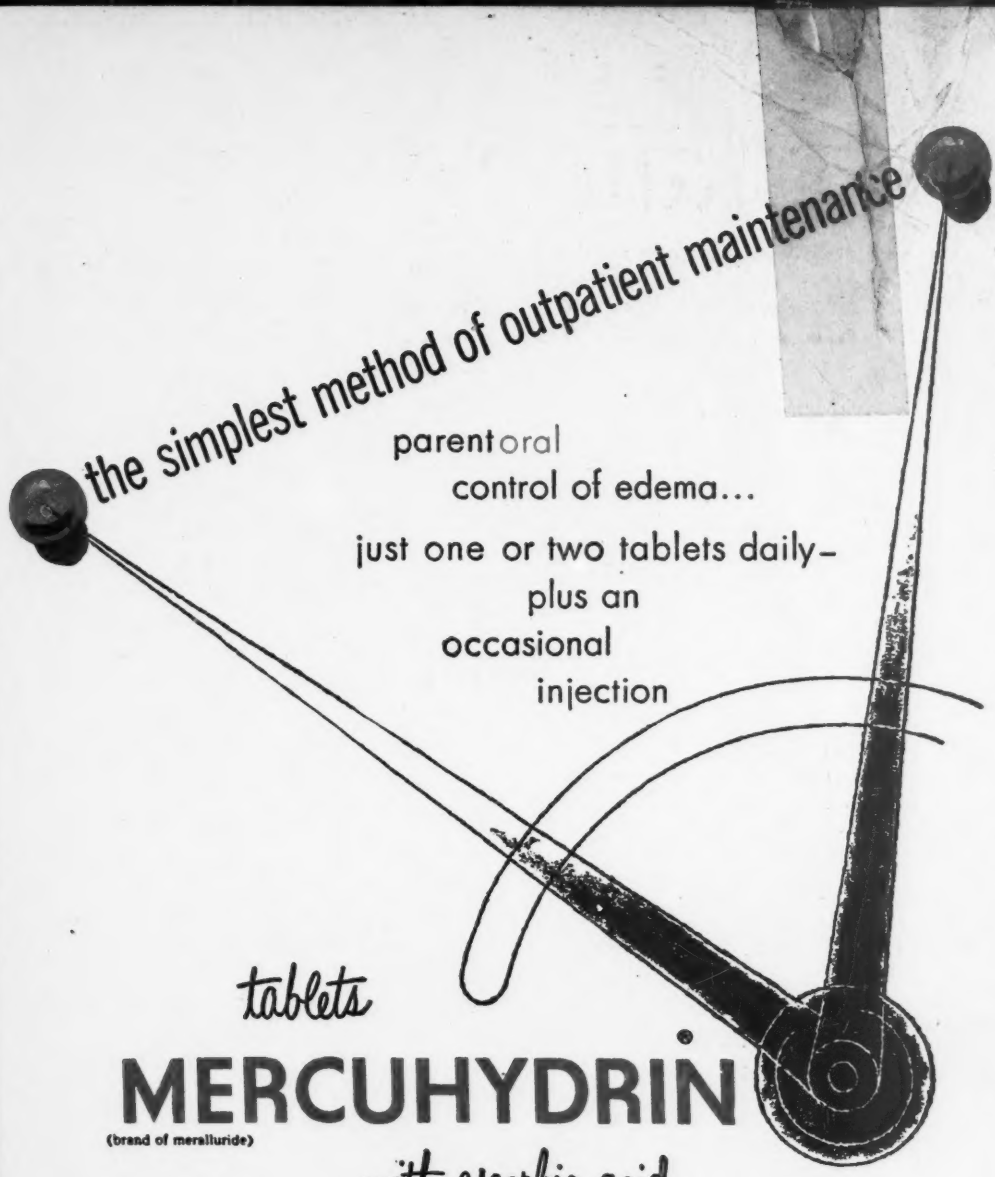
Eliasch, H., Lagerlof, H., and Werko, L.: Diagnosis of Adhesive Pericarditis with Special Reference to Heart Catheterization. Nord. Med. **44:** 1128, 1950.

Three cases of chronic pericarditis were studied with heart catheterization. In two of these cases the diagnosis was made by a typical clinical picture combined with fluoroscopic evidence of pericardial calcifications. The diagnosis of the third case was obscure, as the patient had high venous pressure and systolic retraction of the ribs but lacked radiographic pericardial calcifications. The heart volume was 820 ml. per square meter. Based on the findings from catheterization, suggesting cardiac tamponade, a pericardial tap was performed and 650 ml. of thick nonpurulent fluid was removed.

Heart catheterization gave almost identical findings in all 3 cases. The tracings corresponded to those of 2 single cases published previously, one by Bloomfield and co-workers and the other by Tybjaerg-Hansen. The right auricular mean pressure was markedly elevated without signs of tricupid insufficiency in the right auricular pulse curve. The right ventricular and pulmonary artery tracings demonstrated high end-diastolic pressures with normal pulse pressures. There was a marked pressure dip early in diastole in the right ventricle, probably caused by traction of the pericardial adhesions, which actively expand the right ventricular cavity at that time. After the dip the pressure increased very little during the rest of diastole. The pressure difference between the right auricle and ventricle was about 15 mm. Hg at the beginning of diastole. This pressure gradient produces a rapid inflow of blood into the right ventricle. The systolic retraction of the ribs in the area of the apex was recorded by apex cardiograms. The expansion of the chest wall and the relaxation of the ventricles were found to occur synchronously.

AUTHORS





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